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PROGRESSIVE FACIAL HEMIATROPHY

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An intense and widespread interest has been manifested in the disease described by Parry, in 1825, and by Romberg, in 1846, and named by Eulenburg, in 1871, progressive facial hemiatrophy. In recent years many articles have appeared on this subject in English, German and French. Among these the monographic work of Archambault and Fromm [1] is outstanding. Not only the neurologist but the internist, the pediatrician, the dermatologist, the surgeon, the ophthalmologist and the cosmetologist have contributed to the literature on this subject. This fact is the more remarkable since progressive facial hemiatrophy hardly presents diagnostic or therapeutic problems of magnitude. It is rather the great variety of clinical features and the pathogenesis of this puzzling disease that have attracted such widespread attention. From this standpoint the following clinical observations are noteworthy.

REPORT OF CASES

CASE 1 (National Hospital Queen Square, London, service of the late S. A. K. Wilson).—The patient was a 20 year old girl. Her complaints were: wasting of the right side of the face since the age of 7 years; fits since the age of 15; general headache and knifelike pains through the right side of the head for four or five years, and recent weakness of the whole left side. When she was 4 years old, a "white spot" was noticed on the right side of her forehead, near the midline. This spot gradually spread upward to the scalp, which became completely bald in that area. When she was 7 years old, it was noticed that the right side of the head sank in; for the four years prior to her admission to the hospital this depression had remained stationary. At the age of 7 she had for the first time a sudden attack of a tight feeling spreading up from the left thumb to the shoulder, the face and down the leg, the left foot being affected last. There was no loss of consciousness. This was followed by pain down the whole left side of the body and by muscular twitchings; sometimes the drawing up started in the toes of the left foot and worked into the left arm and the left side of the face. These attacks occurred once in three or four weeks; each of them left her with weakness of the left side, especially of the left arm, which would abate in one or two days. For hours after an attack her left thumb would turn into the palm of the hand. These attacks ceased one year before her admission. Five years prior to admission the diagnosis of scleroderma was made. The left side was becoming increasingly and permanently weaker. Besides these attacks, she had in the previous three years four severe attacks, which started with a sick feeling in the stomach and giddiness. She had general convulsions and frothing at the mouth and became unconscious; she bit her tongue and was incontinent.

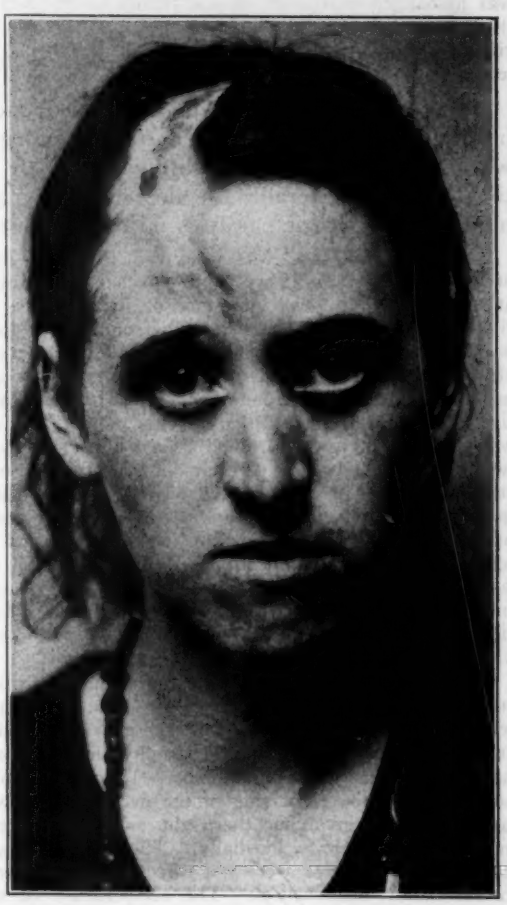

Fig. 1 (case 1).—Right-sided progressive facial hemiatrophy with jacksonian sensory and motor epilepsy on the left side.

Examination revealed pronounced atrophy on the right side of her face, affecting especially the subcutaneous tissues and bone, most noticeably over the forehead (fig. 1). Here there was a furrow to the right of the midline, extending 7.5 cm. back from the hair line. Above the hair line the furrow was completely

To the memory of Samuel Alexander Kinnier Wilson, who suggested this publication.

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1. Archambault, L., and Fromm, N. K.: Progressive Facial Hemiatrophy, Arch. Neurol. & Psychiat. 27:529 (March) 1932.

hairless and covered with yellowish brown scales. The skin over the furrow was paper thin, appeared darker, was glossy, showed fine wrinkling and was attached to the bone. Fine subcutaneous vessels were visible in the area of the furrow. The atrophy on the medial edge of the furrow was greater than on the lateral edge. The furrow continued down the right side of the face to the tip of the nose. The atrophy tapered downward. The upper lip was thinner on the right side than on the left. The skin on the right cheek was normal. The iris of the right eye was darker than that of the left eye. Otherwise there were no motor, sensory or vasomotor disturbances; the muscles were not involved. Electric irritability of the muscles was essentially normal. The cranial nerves were normal. The grip of the left hand was weaker than that of the right. The brachioradial and the triceps reflex were stronger on the left than on the right. There was associated movement of the thumb on bending of the fingers of the left hand; none appeared on the right. Abdominal skin reflexes were weaker on the left side than on the right.

Summary. — Pronounced right-sided facial hemiatrophy was present in a 20 year old girl, with sensory and motor jacksonian epilepsy on the left side, generalized epileptic attacks and mild signs of spastic paralysis on the left side.

CASE 2.—This case was described in detail in a previous paper.[2] A 19 year old rancher had noticed at the age of 10 years thinning of his hair on the right side of his head, beginning in front and creeping backward. At the age of 14, when the bald spot was already conspicuous, it was noticed that the right cheek had become thinner. Four years prior to his admission a diagnosis of tuberculous uveitis of the right eye was made. For a year he had been having attacks of twitching, which first were limited to the third, fourth and fifth fingers of his left hand. Later, this twitching spread to the left forearm and then to the left arm. Such attacks were occasionally followed by loss of consciousness and by incontinence of urine. In the last half-year the twitching in the third to fifth finger and in the left forearm became nearly constant. More violent attacks occurred three or four times a week, with twitching of the whole left arm.

Examination revealed that he had no complaints other than twitching of the left arm. There was pronounced hemiatrophy of the right side of the face. The skin showed no essential changes. Atrophy involved only the subcutaneous tissues and bone. There were pigment spots on the right side of the neck. There was partial alopecia involving the right side of the head and the right eyebrow medially. The right ear was normal. The muscles were not affected. There were no vasomotor disturbances. The temperature of the skin, as well as its reaction to mechanical stimuli, was the same on both sides. Histologic examination of specimens of the skin and bone taken on trepanation over the area of the alopecia revealed no essential changes. Ophthalmologic examination revealed remnants of tuberculous uveitis on the right side. The cranial nerves were normal. There was a slight increase of the deep reflexes of the left arm; sensibility was normal. There were constant fine twitchings of the fourth and fifth fingers, which spread to the flexors of the hand and at times to the flexors of the forearm. Attacks of violent tonic and clonic twitchings of the left arm, lasting one and a half minutes and not accompanied with loss of consciousness, occurred fifteen times or more a day. These attacks varied in intensity and occasionally culminated in grand mal attacks, with loss of consciousness, general convulsions, incontinence and ensuing deep sleep.

During the three weeks' observation in the hospital the number of attacks increased; the small ones occurred from sixty to seventy times a day and resisted all therapy. The surgical procedure, namely, extirpation of the primary cortical cramp center from which, on electric stimulation, flexion of the fourth and fifth fingers could be elicited, brought the attacks to a stop, and the patient was able to return to work.

In the nine months which followed this operation he experienced seven attacks, with twitching of the left shoulder. Examination ten years later revealed that the hemiatrophy had remained stationary. The patient had regained good strength in the left hand but was awkward in fine finger movements. The attacks had ceased.

Summary.—Right-sided progressive facial hemiatrophy occurred in a 19 year old boy, starting at the age of 10. He had had jacksonian epilepsy for one year prior to observation; it had begun in the fingers of the left hand and was of the character of epilepsia partialis continua of Kojevnikoff.

CASE 3 (University of California Hospital, neurosurgical service of Dr. H. C. Naffziger).—A man aged 23 had been operated on at the age of 11 years for an undescended right testicle. He had been having general epileptic attacks since the age of 6 years. These attacks had never offered any localizing clue. When the patient was about 7 years of age, his parents noticed retardation in the growth of the right side of his face; this did not cause the slightest discomfort. The progress, which was very slow, ceased two or three years prior to his admission to the hospital.

The patient showed very pronounced atrophy of the right side of the face, with loss of hair on the skull in exactly the same area as in cases 1 and 2 (fig. 2). There was further loss of hair on the medial third of the right eyebrow. The ear was not involved. The skin was somewhat thinned over the affected area but was otherwise essentially normal. There was slight atrophy of the right side of the tongue. The right pectoralis major muscle was smaller than the left. The testis and the epididymis on the right side were about one-half to one-third the size of those on the left. The deep reflexes on the left were somewhat more active than those on the right. No pathologic reflexes were demonstrable. Roentgenograms showed that the entire right half of the cranium was less developed than the left.

CASE 4.—A woman 26 years of age stated that when she was 3 years old it was noticed that her left cheek "went in." The indentation increased very slowly until two years prior to examination, when progress ceased. The patient had no discomfort. She showed very pronounced left-sided facial hemiatrophy, without involvement of the hair or skin (fig. 3). The subcutaneous vessels on the forehead were visible through the skin, which showed some discoloration but no definite pathologic changes. On the left side of the face the muscles supplied by the facial nerve and the masseter muscle showed some atrophy but no functional impairment.

2. Wartenberg, R.: Zur Klinik und Pathogenese der Hemiatrophia faciei progressiva, Arch. f. Psychiat. **74**:602, 1925.

Fig. 2 (case 3).—Right-sided progressive facial hemiatrophy with general epileptic attacks.

Fig. 3 (case 4).—Left-sided progressive facial hemiatrophy without involvement of the hair or skin.

CASE 5.—Left-sided facial hemiatrophy of very slow progression was slightly corrected by plastic operation. The hair, muscles and skin were not involved; only the homolateral half of the tongue showed marked atrophy (fig. 4).

CASE 6.—A 33 year old housewife noticed, twelve years prior to examination, a small dent on the right side of the forehead, 1 fingerbreadth lateral to the midline. The indentation increased in depth and spread upward very slowly. Five or six years prior to examination she noticed an indentation in her right cheek, which since then has slowly increased in depth. She has never felt any discomfort relative to her face. The atrophy was more marked over the forehead and on the medial edge of the area involved than on the lateral edge (fig. 5). The fat of the cheek had diminished

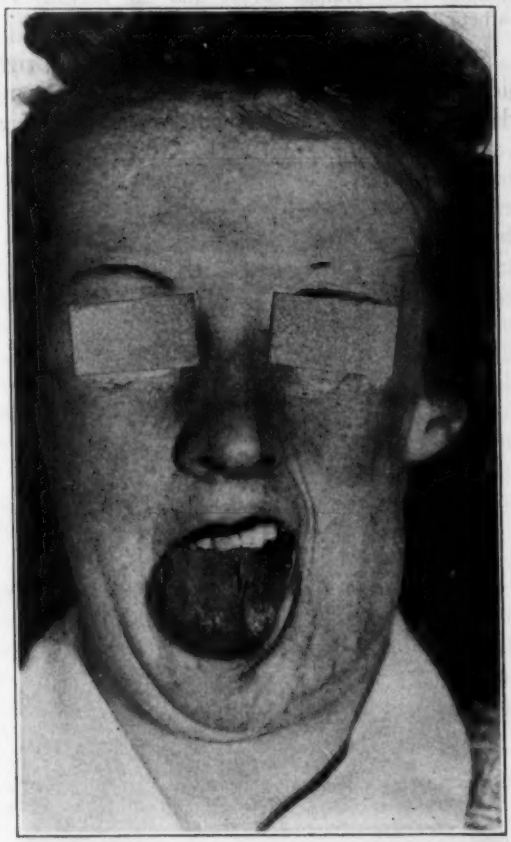

Fig. 4 (case 5).—Left-sided progressive facial hemiatrophy with pronounced homolateral atrophy of the tongue.

strikingly. The skin and muscles were not affected. There was dandruff on the right side of the scalp but none on the left. There were no disturbances of the sympathetic nervous system, and the fifth nerve was normal. Roentgenographic examination showed normal bones. The right eye exhibited no signs of infection, but there were more and larger vessels around the limbus of the right eye than around that of the left eye. On examination with the slit lamp the capillaries of the right eye were found to be larger than those of the left.

Summary.—Right-sided facial hemiatrophy has produced in the course of twelve years only

mild changes in the fat and subcutaneous tissues, leaving the skin intact.

CASE 7.—A 27 year old housewife had noticed very slow shrinking of the right cheek, which had started about nine years ago. The cheek itched occasionally; otherwise there were no complaints. There was slight atrophy of the skin and subcutaneous tissues above and outside the angle of the mouth on the right side in an area 2 by 1 cm. (fig. 6). The skin in this area was brown, atrophic and crinkled. The fat pad on the right cheek was diminished distinctly. On the right side of the forehead, 1 fingerbreadth from the midline above the right eyebrow, there was a fine streak where the skin was shiny, slightly atrophic and crinkled. This area was about ⅓ finger length and ½ fingerbreadth. The cranial nerves and the cervical sympathetic trunk were normal.

Summary.—In the course of nine years, right-sided facial hemiatrophy has produced only mild changes in the skin of the forehead and slight changes in the skin and subcutaneous tissues of the corner of the mouth.

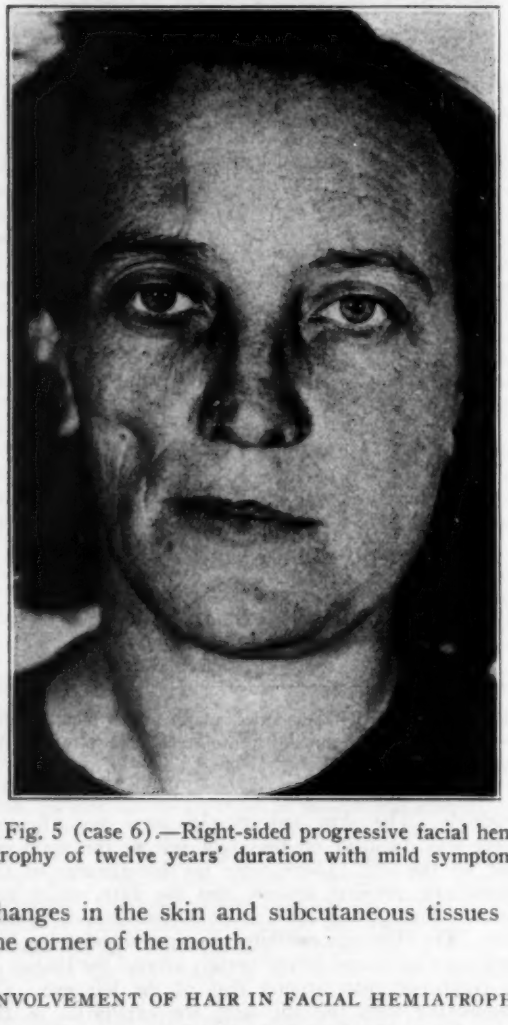

Fig. 5 (case 6).—Right-sided progressive facial hemiatrophy of twelve years' duration with mild symptoms.

INVOLVEMENT OF HAIR IN FACIAL HEMIATROPHY

Involvement of the hair of the scalp was a striking feature in the first 3 cases presented here. The affected side showed circumscribed complete alopecia. Alopecia of similar location and extent has been reported in some published cases. Mention may be made of the cases of Cords,[3] Dana,[4] Harris,[5] Klingmann,[6] Lloyd,[7] Montanaro and Pierini,[8] Osborne[9] and Tauber and Goldman.[10] Involvement of the hair in the form of alopecia or of canities (blanching) was mentioned by Bernstein,[11] Bory,[12] Diller,[13] Jendrassik,[14] Joss-

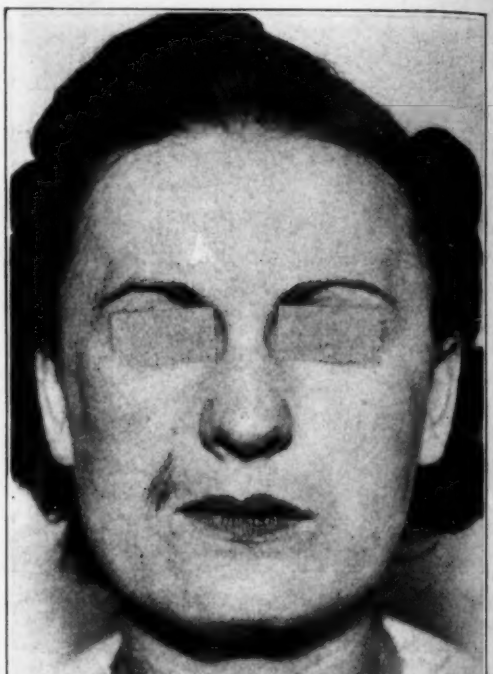

Fig. 6 (case 7).—Right-sided progressive facial hemiatrophy of nine years' duration, with only mild involvement of the skin of the forehead and cheek.

3. Cords, R.: Strichförmige Gesichtsatrophie und Auge, Ber. d. deutsch. ophth. Gesellsch. **47**:53, 1928.

4. Dana, C. L.: Textbook of Nervous Diseases, ed. 10, New York, William Wood & Company, 1925, p. 606.

5. Harris, W.: Neuritis and Neuralgia, New York, Oxford University Press, 1926, pp. 243 and 283.

6. Klingmann, T.: Facial Hemiatrophy, J. A. M. A. **49**:1888 (Dec. 7) 1907.

7. Lloyd, J. H.: Hemifacial Atrophy, M. News, Philadelphia **67**:604, 1895.

8. Montanaro, J. C., and Pierini, L. E.: Hemiatrofia facial progresiva, Semana méd. **1**:704, 1938.

9. Osborne, E. D.: Morphea Associated with Hemiatrophy of the Face, Arch. Dermat. & Syph. **6**:27 (July) 1922.

10. Tauber, E. B., and Goldman, L.: Hemiatrophia Faciei Progressiva, Arch. Dermat. & Syph. **39**:696 (April) 1939.

11. Bernstein, E.: Hemiatrophia alternans facialis progressiva mit halbseitiger Alopezia, Pigmentverschiebung und Hautatrophie, Dermat. Wchnschr. **90**:235, 1930.

(Footnotes continued on next page)

mann,[15] Lauber,[16] Léri,[17] Loewy-Hattendorf,[18] Meyer,[19] Ratner,[20] Stief and Tanka,[21] Stiefler,[22] Vassilevski,[23] Vivado,[24] Mailhouse [25] and others. When half of the lip is affected, it may become completely hairless, whereas the mustache grows naturally on the healthy side (Blumenau [26]). Also, the eyelashes and the hair of the eyebrow on the affected side may be more or less absent. Bernstein [11] reported a case of progressive facial hemiatrophy with "unilateral alopecia," so conspicuous was the loss of hair.

In the course of progressive facial hemiatrophy, the hair of the scalp and face is involved not only frequently but very early. This involvement of the hair may precede the appearance of any other sign of the disease, as shown in cases 1 and 2. In the older literature many cases were reported in which falling out or blanching of the hair was the initial manifestation. From pertinent cases published recently, reference may be made to the cases of Cheever,[27] Jossmann,[15] Archambault and Fromm [1] (case 3) and Wolfe and Weber.[28]

12. Bory, M. L.: Un cas d'hémiatrophie faciale progressive avec sclérodermie partielle du cuir chevelu, Bull. Soc. franç. de dermat. et syph. **36**:863, 1929.

13. Diller, T.: A Case Exhibiting Symptoms of Facial Hemiatrophy and Jacksonian Sensory Epilepsy, J. Nerv. & Ment. Dis. **20**:284, 1895.

14. Jendrassik, E.: Ueber die Hemiatrophia faciei, Deutsches Arch. f. klin. Med. **59**:222, 1897.

15. Jossmann: Hemiatrophia faciei, Zentralbl. f. d. ges. Neurol. u. Psychiat. **55**:348, 1930.

16. Lauber, H.: Ein Fall von Hemiatrophia facialis progressiva, Ztschr. f. Augenh. **57**:492, 1925.

17. Léri, A.: Hémiatrophie faciale avec paralysies multiples des nerfs crâniens, Bull. et mém. Soc. méd. d. hôp. de Paris **37**:1594, 1921.

18. Loewy-Hattendorf, E.: Demonstration, Zentralbl. f. d. ges. Neurol. u. Psychiat. **27**:413, 1922.

19. Meyer, H. E.: Ueber Hemiatrophia faciei und totalis, Med. Klin. **32**:352, 1936.

20. Ratner, T.: Ueber einen Fall von Hemiatrophia cruciata progressiva, Deutsche Ztschr. f. Nervenh. **97**: 304, 1927.

21. Stief, S., and Tanka, D.: Rare Case of Hemiatrophia Faciei, Orvosi hetil. **69**:459, 1925; abstracted, Zentralbl. f. d. ges. Neurol. u. Psychiat. **41**:649, 1925.

22. Stiefler, G.: Ueber die Hemiatrophia faciei progressiva bilateralis, Jahrb. f. Psychiat. u. Neurol. **51**: 277, 1934.

23. Vassilevski, M.: A Case of Progressive Hemiatrophy of the Face, Shoulder Girdle and Hand, Sovet. nevropat. **2**:78, 1933.

24. Vivado: Sobre un caso de hemiatrofia de origen simpatico, Rev. méd. de Chile **56**:1066, 1928.

25. Mailhouse, M.: Facial Hemiatrophy, J. Nerv. & Ment. Dis. **28**:225, 1901.

26. Blumenau, L.: Unilateral Atrophy of the Face, Vestnik psikhiat. i nevropat. **7** (pt 1):219, 1889-1890; abstracted, J. Nerv. & Ment. Dis. **15**:259, 1890.

27. Cheever, A. W.: A Case for Diagnosis (Congenital Syphilis? Hemiatrophy?), Arch. Dermat. & Syph. **34**:297 (Aug.) 1936.

28. Wolfe, M. C., and Weber, M. L.: Progressive Facial Hemiatrophy, J. Nerv. & Ment. Dis. **91**:595, 1940.

The fact that alopecia may precede the atrophy is diagnostically important, since for this reason progressive facial hemiatrophy must be considered as a possible cause of obscure circumscribed alopecia. Thus, the statement of Oppenheim [29] that the hair of the head is almost never affected in cases of hemiatrophy is untenable.

The location of the alopecia and canities on the skull and on the face is remarkable. The involvement of the hair does not extend to the midline but occupies an area which is best called the "paramedian area." This area consists of a strip about 2 fingerbreadths in width, lateral and parallel to the midline, over the forehead and the whole face, involving the inner aspect of the eyebrow, the eyelashes and the outer part of the mouth. The atrophy is most pronounced on the medial edge of this strip. Numerous pictures and descriptions of facial hemiatrophy show again and again the localization of alopecia, canities and the atrophic process, as seen in the first 3 cases reported here. Reference may be made to cases of Nikitin,[30] Flint,[31] Romberg,[32] Leskowski [33] and Bramwell.[34] Some authors emphasize that the atrophy does not reach the midline but stops at a distance of 1 or 2 fingerbreadths from it. Therefore, the statement of Curschmann [35] that the atrophic process always ends exactly in the midline is hardly tenable. Neither is it correct to speak of "the usual strictly midline delimitation of the lesion from the normal side" (Cox and Maclure [36]).

Not only is the atrophy most pronounced in the paramedian area, but the atrophic process usually starts there—at the outer part of the mouth, the inner part of the eye and on the forehead, lateral to the midline (Archambault and Fromm,[1] Diller,[13] Jendrassik [14] and Walsh [37]).

29. Oppenheim, H.: Lehrbuch der Nervenkrankheiten, ed. 7, Berlin, S. Karger, 1923, p. 2167.

30. Nikitin, M. P.: Case of Atrophy in the Area of the First Branch of the Trigeminal Nerve, Obozr. psikhiat., nevrol. **15**:70, 1910.

31. Flint, G.: Case of Partial Atrophy of Right Side of Face, Tr. Ophth. Soc. U. Kingdom **52**:308, 1932.

32. Romberg: Klinische Ergebnisse, Berlin, A. Förstner, 1846, p. 75.

33. Leskowski: Hemiatrophia facialis, Neurol. Centralbl. **25**:1008, 1906.

34. Bramwell, B.: Atlas of Clinical Medicine, Edinburgh, T. & A. Constable, 1891, p. 97.

35. Curschmann, in von Bergmann, G., and Staehelin, R.: Handbuch der inneren Medizin, ed. 2, Berlin, Julius Springer, 1926, vol. 5, pt. 2, p. 1482.

36. Cox, L. B., and Maclure, A. F.: Facial Hemiatrophy, Australian & New Zealand J. Surg. **5**:68, 1935.

37. Walsh, F. B.: Facial Hemiatrophy, Am. J. Ophth. **22**:1, 1939.

ABORTIVE FACIAL HEMIATROPHY

The fact that the pathologic changes associated with hemiatrophy are found mostly in the paramedian area is of diagnostic importance, since thereby early stages of the disease and the condition to be designated as "abortive progressive facial hemiatrophy" may be recognized. The term "progressive" must not be taken literally. The atrophy does not progress indefinitely, and the final stage never is a complete atrophy of the tissues. The disease progresses for a number of years and then becomes stationary for the remainder of life. The development of progressive facial hemiatrophy may thus cease at any point at any time. The case of Kahler [38] might be mentioned in which the atrophy had developed in the tenth year of life and had not shown any progression at the fifty-fourth year. In some of these cases of arrested progression the process remained limited essentially to the forehead (Lloyd,[7] Bini [39]). In discussing a case in which the differential diagnosis of scleroderma and progressive hemiatrophy had been made, Pick [40] rejected the latter diagnosis because the disease had shown no progression for twenty-seven years. Such reasoning is not correct since the existence of progressive facial hemiatrophy with arrested progression must be assumed. In many cases of this type the visible changes may be so mild and inconspicuous that they escape notice on the part of the patient or, if noticed, are disregarded. The changes are to be found in such cases in the paramedian area, in the same location in which the pronounced alopecia and atrophy are seen in cases of the fully developed disease.

It is justifiable to assume that cases 6 and 7, previously described, also belong here. There is, of course, no such sharply defined entity as abortive progressive facial hemiatrophy. The illustrations clearly demonstrate the numerous transitional forms of facial hemiatrophy and show the wide range of clinical symptoms of the disease.

CASE 8.—A man 71 years of age noticed about nineteen years ago a dimple on the forehead at the hair line, 1 fingerbreadth to the right of the midline. This dimple slowly developed downward to the eyebrow. About ten years prior to examination he noticed on the forehead, and parallel to this line, another dimple, 1 fingerbreadth lateralward and not so deep. The development had been very slow. The condition had been stationary for the past six or seven years. The illustration (fig. 7) shows very slight atrophy of the subcutaneous tissue on the forehead, exactly in the area grossly affected in the first 3 cases of fully developed facial hemiatrophy. The skin was normal, and roentgenograms of the skull showed that the bones were normal.

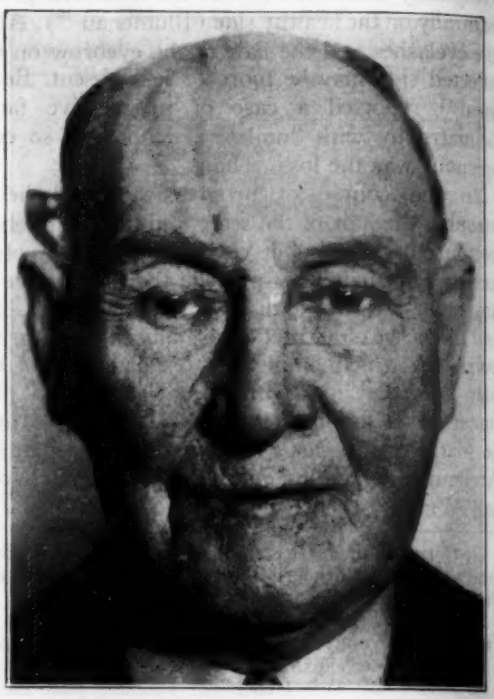

Fig. 7 (case 8).—Right-sided abortive progressive facial hemiatrophy of nineteen years' duration, with mild manifestations on the forehead only.

CASE 9.—A 24 year old rancher had noticed seven years previously a dimple in the forehead, to the right of the midline; it had slowly progressed until the last three or four years, when it became stationary. Figure 8 shows a cleft in the forehead, directly to

Fig. 8 (case 9).—Right-sided abortive progressive facial hemiatrophy of seven years' duration, with manifestations on the forehead.

38. Kahler, O.: Ein Fall von beschränkter neurotischer Atrophie im Gesichte, Prag. med. Wchnschr. **6**:53, 1881.

39. Bini, L.: Sull' emiatrofia facciale progressiva, Riv. sper. di freniat. **61**:19, 1937.

40. Pick, W.: Sclerodermie en coup de sabre mit osteoporotischer Zone im Stirnbein oder Hemiatrophia faciei? Arch. f. Dermat. u. Syph. **167**:543, 1933.

the right of the midline. On palpation the cleft appeared deep, but with no apparent involvement of the bone. The skin over this area was adherent to the underlying tissues. It did not show any definite changes. No roentgenograms were made. The atrophic process in this case was nearer the midline than in the other cases.

Case 10.—A housewife 47 years of age came to the clinic because of functional nervous disturbances; she did not mention the condition of her skin. On inquiry, she revealed that twenty years previously the medial side of the right eyebrow showed gradually increasing sparseness of the hair. This condition had remained stationary during the past three years. Examination of the glabella (fig. 9) showed normal hair, which extended as far as 0.5 cm. to the right of the midline. From here, the right eyebrow showed complete loss of hair to the middle, with no changes in the skin. The medial portion of the eyelashes of the right eye was completely absent. Otherwise the lid was normal. The hair on the upper lip showed no difference between the right and the left side. There were two nevi pilosi, one on the chin and the other on the front of the neck, ½ fingerbreadth above the sternum. Both were at the same distance from the midline—about 0.5 cm. to the right.

Examination of the scalp showed a completely hairless area on the top of the head; this was 4 cm.

Fig. 9 (case 10).—Right-sided abortive progressive facial hemiatrophy of twenty years' duration, showing changes in one eyebrow. Two nevi pilosi are present on the side of the hemiatrophy in the paramedian area.

long and 1 cm. wide, starting 0.5 cm. to the right of the midline (fig. 10). Here the skin was atrophic, thin as paper and crinkled. On palpation there was a definite indentation in this area. Sebaceous glands were present. Separated from this spot, in front of and lateral to it, was another hairless area, as the illustration shows. The patient was completely unaware of her bald spots.

There is hardly any doubt that cases such as 8 9 and 10 are classified best as instances of abortive facial hemiatrophy.

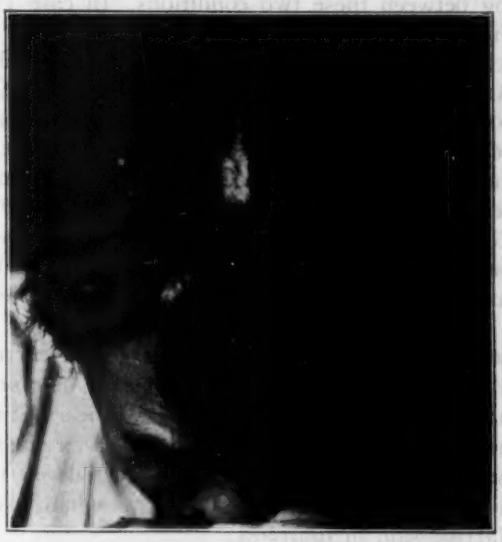

Fig. 10 (case 10).—Right-sided abortive progressive facial hemiatrophy, showing changes of the hair on the skull.

PROGRESSIVE FACIAL HEMIATROPHY AND SCLERODERMA

In the literature (reviewed by Möbius,[41] Marburg,[42] Lauerbach[43] and Wohning[44]) the intimate connection of hemiatrophy and scleroderma has been much discussed. Cassirer[45] expressed the opinion that facial hemiatrophy was a definite form of scleroderma with special localization, as did Chasanow[46] and Archambault and Fromm.[1] Kroll[47] emphasized that a differential diagnosis between facial hemiatrophy and scleroderma may be impossible. When scleroderma is located in the face, it is called morphea, or scleroderma *en coup de sabre*. This expression

41. Möbius, P. J.: Der umschriebene Gesichtsschwund, Vienna, A. Hölder, 1895.

42. Marburg, O.: Die Hemiatrophia facialis progressiva, Vienna, A. Hölder, 1912.

43. Lauerbach, F.: Ein Fall von Hemi-Hypoplasie des Gesichtes und der Zunge, mit kritischen Bemerkungen zum Symptomenbild der Rombergschen Hemiatrophia faciei, Arch. f. Dermat. u. Syph. **144**:285, 1923.

44. Wohning, M.: Hemiatrophia faciei und Sklerodermie, Inaug, Dissert., Freiburg i. Br., N. D.

45. Cassirer, R.: Die vasomotorisch-trophischen Neurosen, Berlin, S. Karger, 1912.

46. Chasanow, M.: Beiträge zur Aetiologie der Hemiatrophie des Gesichtes, Ztschr. f. d. ges. Neurol. u. Psychiat. **140**:473, 1932.

47. Kroll: Die neuropathologischen Syndrome, Berlin, Julius Springer, 1929.

is highly appropriate, since the patient looks as if he had received a stroke over his forehead with a sword. The title of an article by Pick,[40] "Scleroderma *en coup de sabre* with Osteoporotic Zone in the Frontal Lobe, or Facial Hemiatrophy?" illustrates the difficulty in differentiating between these two conditions. In case 1 of this series, the condition, first diagnosed as scleroderma, developed into classic hemiatrophy. According to some authors (Ben,[48] Bory,[12] Osborne[9] and Truffi[49]), hemiatrophy and scleroderma may occur simultaneously in the face of the same patient, or local scleroderma may develop into hemiatrophy (Rosenthal[50]). Cords[3] called *sclerodermie en coup de sabre* a "streaklike facial atrophy." Ehrmann and Brünauer[51] compiled the literature on this subject.

It is remarkable that scleroderma *en coup de sabre* is located in the paramedian area, corresponding exactly to the area of loss of hair seen in the first 3 cases of the present series. Stühmer[52] pointed out that in scleroderma *en bandes* the disturbance is apparently located in the median, but is actually in the paramedian, area. Harris[5] said of morphea:

> A noteworthy point is that the trophic loss described as greyness, baldness and atrophy of the bones of the face and the skin does not extend as far inward as the middle line, but ceases about the line of the supraorbital notch.

I should hardly hesitate to ascribe the morphea in his case to abortive progressive facial hemiatrophy with typical localization of loss of hair in the paramedian area. The same applies to the cases of Mitchell,[53] Ehrmann and Brünauer[51] and Spillmann.[54] Flint,[31] in describing a case of facial hemiatrophy, spoke of a *coup de sabre* deformity. In some cases of facial hemiatrophy the *sclerodermie frontale en coup de sabre* constituted an integral part of the whole clinical picture (Bory[12]). Numerous other reports could be mentioned illustrating the localization of what is known as scleroderma in the paramedian area in which alopecia, blanching of the hair and atrophy are found in cases of facial hemiatrophy. Therefore, the assumption is justified that what has been known as scleroderma *en coup de sabre* is nothing but an abortive form of progressive facial hemiatrophy, the progression of which stopped very early. The similarity of these two conditions is clearly seen in the reports of Osborne,[9] O'Leary and Nomland[55] and Tauber and Goldman.[10]

BORDERLINE FORMS OF PROGRESSIVE FACIAL HEMIATROPHY

It is most interesting that besides hemiatrophic and sclerodermatous lesions, other pathologic conditions are located often in the paramedian area, such as nevi (Bailey,[56] Meirowsky[57] [his figures 7, 38, 39]), moles (Roussy and associates[58]), congenital partial whiteness of the eyelashes (Streatfeild[59]) and grayness of the hair (Cheatle[60]). From observations, I, too, gained the definite impression that this paramedian area represents a place of predilection for malformation and other morbid conditions of the skin, of many varieties. All these may be classified as "paramedian facial cutaneous dystrophy." In some of these cases the condition may be regarded as abortive facial hemiatrophy, and in some as congenital malformation of the skin; in some only changes in the skin or hair are seen; in some the disease is slightly progressive; in some the condition remains unchanged, but in all cases the dystrophy is located on a streak parallel to the median line and at some distance from it. Examples of such a paramedian facial cutaneous dystrophy are given here.

Case 11.—A 42 year old laborer showed discoloration of his facial hair, of which he was hardly aware (fig. 11). On the left side, the inner fourth of his eyebrow and eyelashes was white; the rest was dark. There was much white on the left side of his mustache, especially on the outer part of the lip. There were

48. Ben, F.: Hemiatrophia faciei und Sklerodermie, Dermat. Wchnschr. **83**:1366, 1926.

49. Truffi, G.: Emiatrofia facciale sinistra con sclerodermia circoscritta, Dermosifilografo **8**:90, 1933.

50. Rosenthal, O.: Ueber einen Fall von partieller Sklerodermie, mit Uebergang in halbseitige Gesichtsatrophie, combiniert mit alopecia areata, Berl. klin. Wchnschr. **26**:755, 1889.

51. Ehrmann, S., and Brünauer, St. R.: Sclerodermie, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1931, vol. 8, pt. 2, p. 717.

52. Stühmer, in discussion on Vohwinkel: Sclerodermie en bandes et en plaques, Zentralbl. f. Haut- u. Geschlechtskr. **27**:586, 1928.

53. Mitchell, J. H.: Scleroderma Circumscriptum en Coup de Sabre, Arch. Dermat. & Syph. **34**:115 (July) 1936.

54. Spillmann, L.: Sclérodermie lardacée en coup de sabre de la région frontale: Crises épileptiformes concomitantes, Rev. méd. de l'est **30**:597. 1898.

55. O'Leary, P., and Nomland, R.: A Study of One Hundred and Three Cases of Scleroderma, Am. J. M. Sc. **180**:95, 1930.

56. Bailey, P.: Intracranial Tumors, Springfield, Ill, Charles C Thomas, Publisher, 1933, case XX, fig. 81.

57. Meirowsky, E.: Die angeborenen Muttermäler und die Färbung der menschlichen Haut im Lichte der Abstammungslehre, Jena, Gustav Fischer, 1920, figs. 7, 38 and 39.

58. Roussy, G.; Lévy, G., and Rosenrauch, C.: L'origine médullaire de certaines rétractions de l'aponévrose palmaire [fig. 2], Ann. de méd. **31**:21, 1932.

59. Streatfeild, J. F.: Observations on Some Congenital Diseases of the Eye, Lancet **1**:263, 1882.

60. Cheatle, G. L.: The Incidence of the Hair's Greyness, Brit. M. J. **2**:176, 1905.

no other changes in the hair or skin. The spots in which the eyebrow, eyelashes and mustache on the left showed the greatest discoloration were on a vertical line, all at the same distance from the midline.

Case 12.—A 60 year old man showed very mild white discoloration of the medial portion of his left eyebrow and conspicuous and nearly complete white discoloration of the medial part of the lashes of his

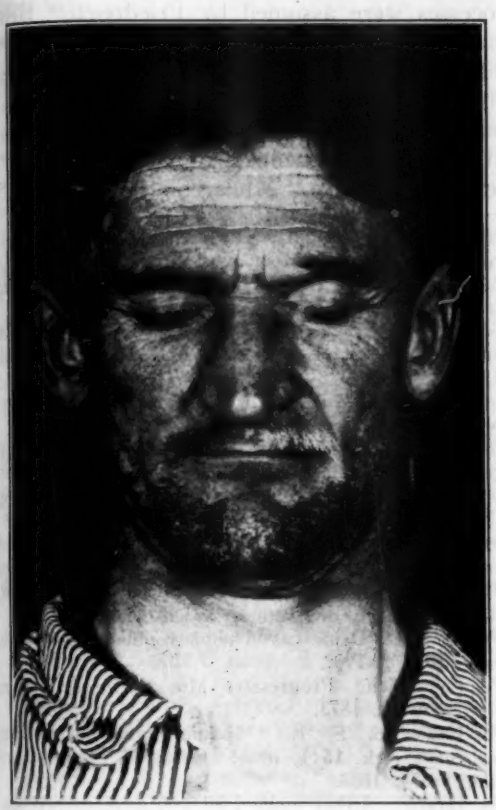

Fig. 11 (case 11).—Left-sided blanching of the eyebrows, eyelashes and mustache in the paramedian area.

Fig. 12 (case 12).—Left-sided blanching of the eyelashes in the paramedian area.

left eye (fig. 12). He could give no definite information as to the beginning or the course of this discoloration.

Case 13.—A 19 year old youth showed some spots of white in the hair on the left side of his head, in the temple area. Most evident was the discoloration of the hair on the medial edge of his left eyebrow, in the paramedian area.

Case 14.—A 45 year old man showed a pigmented area on the left side of his forehead close to the midline and running parallel to the midline from the hair line to the eyebrow (fig. 13). There were no other changes. The patient stated that the pigmentation might have developed within the last few years.

Case 15.—A 42 year old man showed a pigmented area, without any other changes in the skin, on the right side of the forehead, beginning in the midline and extending about 1 fingerbreadth (fig. 14). Details of development are not available, but the condition certainly was not congenital.

Cognizance is taken of these peculiar neurodermatologic changes, although their pathophysiologic significance cannot be appraised exactly. It is especially difficult to say how far one may go in any one case in classifying the condition as

Fig. 13 (case 14).—Nevus flammeus on the left side of the forehead parallel to the midline.

Fig. 14 (case 15).—Nevus flammeus on the right side of the forehead near the midline in the same area in which abortive facial hemiatrophy is seen in figure 7 (case 8).

abortive facial hemiatrophy. But there is little doubt that in every single case there is some relation to this disease and that, by paying attention to changes in the skin in the paramedian area of the face, one might be able to diagnose the disease in its very early stages.

PARAMEDIAN AREA

The location and extent of this paramedian area are peculiar. They do not correspond to any peripheral branch of the trigeminus nerve or to onion-peel-like areas in cases of lesions of

the nucleus of the trigeminus nerve. There is nothing that would suggest a connection with the embryonic closure lines of the face (Fischer [61]), nor does the paramedian area correspond to the area in which the various branches of the trigeminus nerve become cutaneous. The median line extends more medially than the points of emergence of the trigeminal branches. The first hemiatrophic manifestations often are found on the forehead in an area remote from the point at which the first branch of the fifth nerve becomes cutaneous.

The following hypothesis is a possible interpretation of the peculiar site of this paramedian area: In hemiatrophy the central part of the face is affected either not at all or late in the disease. The part first and most intensively affected is, as has been seen, a vertical streak running parallel to the midline and at some distance lateral to it. The median part of the face obtains its nerve supply from both sides. It is known that the cutaneous nerves of the face transgress the median line from both sides. Therefore, the nerve fibers overlap in the middle line to an extent that varies much individually. A rough comparison would be to imagine that in trophic innervation the two vertical halves of the body are joined together in dovetailed fashion, like two pieces of wood with alternate interlocking. The trophism of the middle part of the face is secured from both sides and does not suffer from a unilateral lesion. But the area of the skin located laterally, in which the double innervation ceases and the unilateral innervation begins, must be, so to speak, a weak spot in the trophic innervation and therefore is susceptible to pathologic changes. It is in this paramedian area that one must look for the beginning of hemiatrophic or other pathologic changes.

THE BRAIN IN PROGRESSIVE FACIAL HEMIATROPHY

Striking and significant features of the first 3 cases were the signs and symptoms of involvement of the brain. In the literature frequent mention is made of cerebral manifestations in cases of hemiatrophy. Beer,[62] in 1898, found cerebral symptoms in 15.54 per cent of 148 collected cases. Two kinds of cerebral involvement are recognized. The first is a more or less diffuse involvement of the brain; the second, more significantly, is an involvement of the brain on the side of the hemiatrophy. In the first category belong the cases of Bannister,[63] Bergson,[64] Delamare,[65] Mendel [66] and Romberg,[32] who reported the association of hemiatrophy with mental disease. Arteriosclerosis of the cerebral vessels or encephalomalacia was found by Jolly,[67] Orbison,[68] Parry,[69] Pissling [70] and Touche.[71] Encephalitic processes were assumed by Friedreich,[72] Henschen,[73] Hrach,[74] Meyer,[75] Raymond and Sicard [76] and Tedeschi.[77] A diagnosis of pain of central origin was made by Stief [78] and Wolff.[79] Numerous authors found hemiatrophy associated with migraine (Boenheim,[80] Bruns,[81] Cornu,[82] Herz,[83] Holtzapple,[84] Mollaret,[85] Reiss,[86] Salus,[87]

61. Fischer, O.: Ein Beitrag zur Lehre von der Hemiatrophia facialis progressiva, Monatschr. f. Psychiat. u. Neurol. **14**:366, 1903.

62. Beer, M.: Beitrag zur Kenntnis der Hemiatrophia facialis progressiva, Inaug. Dissert., Königsberg i. Pr., L. Krause & Ewerlein, 1898.

63. Bannister, H. M.: Progressive Facial Hemiatrophy, J. Nerv. & Ment. Dis. **3**:539, 1876.

64. Bergson: De Prosopodysmorphia, Inaug. Dissert, Berlin, Nietack, 1837.

65. Delamare: Contribution à l'histoire de l'aplasie lamineuse progressive de la face, Rec. de mém. de méd. mil. **36**:484, 1880.

66. Mendel, E.: Ein Fall von halbseitiger Gesichtsatrophie, Neurol. Centralbl. **1**:268, 1883.

67. Jolly: Ueber multiple Hirnsklerose, Arch. f. Psychiat. **3**:711, 1877.

68. Orbison, T.: Trophic Hemiatrophia: Complete, J. Nerv. & Ment. Dis. **35**:695, 1908.

69. Parry, C. H.: Collections from unpublished papers, London, Underwood, 1825, vol. 1, p. 478.

70. Pissling: Mitteilungen aus der Praxis, Ztschr. d. k.-k. Gesellsch. d. Ärzte zu Wien **1**:496, 1852.

71. Touche: Deux cas d'hémiatrophie faciale, Rev. neurol. **10**:375, 1902.

72. Friedreich: Progressive Muskelatrophie, Berlin, A. Hirschwald, 1873.

73. Henschen, S. E.: Hemiatrophia progressiva, Nord. med. Ark. **15**:1, 1883; abstracted, Neurol. Centralbl. **1**:374, 1883.

74. Hrach: Ueber einen Fall von angeborener neurotischer Hemiatrophie, Wien. med. Wchnschr. **54**: 343, 1904.

75. Meyer, E.: Totale Hemiatrophie, Neurol. Centralbl. **29**:450, 1910.

76. Raymond and Sicard: Trophonévrose hémiatrophique totale et familiale, Rev. neurol. **13**:593, 1902.

77. Tedeschi: Paralysie spinale infantile aiguë avec hémiatrophie de la face, Rev. neurol. **13**:42, 1905.

78. Stief, A.: Ueber einen Fall von Hemiatrophie des Gesichtes mit Sektionsbefund, Ztschr. f. d. ges. Neurol. u. Psychiat. **147**:573, 1933.

79. Wolff, H. G.: Progressive Facial Hemiatrophy, Arch. Otolaryng. **7**:580 (June) 1928.

80. Boenheim: Zur Pathogenese der Hemiatrophia faciei progressiva, Deutsche Ztschr. f. Nervenh. **65**: 219, 1920.

81. Bruns: Hemiatrophia facialis progressiva, Neurol. Centralbl. **16**:511 1897.

82. Cornu, E.: Contribution à l'étude des migraines et de leurs rapports avec les états épileptiques et délirants, Thesis, Lyon, no. 144, 1902.

83. Herz, M.: Ueber Hemiatrophia facialis progressiva, nebst Mittheilung eines diesbezüglichen Falles, Arch. f. Kinderh. **8**:241, 1886-1887.

84. Holtzapple, cited by Flatau, E., in Lewandowsky, M.: Handbuch der Neurologie, Berlin, Julius Springer, 1914, vol. 5, p. 400.

(Footnotes continued on next page)

Souques and Bourguignon,[88] Oppenheim [29] and Wolff [89]). Of special interest are those cases in which the migraine was localized homolaterally. Wolff reported the case of a 23 year old woman with hemiatrophy of the right side of the face who had been suffering from right-sided migraine headaches since the age of 12 years. The unilateral head pain in Diller's [13] case was "always strictly confined to the right side," the side of the hemiatrophy. Klingmann's [6] patient had hemiatrophy of the right side of the face and complained of constant pain in the right occipital region. The patient in case 1, with hemiatrophy of the right side of the face, had knifelike pains through the right side of her head.

In numerous cases the hemiatrophy was associated with epilepsy. The following authors may be mentioned: Archambault and Fromm,[1] Bost,[90] Bragman,[91] Brunner,[92] Buzzard,[92] Černi,[93] Chasanow,[46] Diller,[13] Donley,[94] Emminghaus,[95] Hallager,[92] Kiely,[96] Kopczynski,[97] Lande,[98] Lauber,[16] MacBride,[99] Merritt, Faber and Bruch,[100] Merzejewsky,[92] M. Meyer,[101] O. B. Meyer,[102] Neustaedter,[103] Osborne,[9] Schultze,[104] Stiefler,[22] Thiel,[105] Vivado,[24] Wolfe and Weber [28] and Zeller.[106] Except in a few cases, as, for instance, in that of Bragman [91] and in my case 3, the epilepsy was a late manifestation. In the light of the foregoing discussion regarding the relationship of scleroderma *en coup de sabre* and hemiatrophy, it is remarkable that Spillmann [54] and Josefowitsch [107] reported the association of epilepsy and scleroderma.

Tauber and Goldman [10] and Pollock [108] expressed the belief that of all complications of hemiatrophy, epilepsy is the most frequent. This statement could hardly be maintained, even in the light of the numerous cases cited. On the other hand, one can hardly subscribe to the opinion of Archambault and Fromm,[1] who stated:

> There is nothing astonishing in the fact that, rare as it is, facial hemiatrophy should occasionally appear in a person suffering from so common a disease as epilepsy.

That the combination of epilepsy and hemiatrophy cannot be regarded as purely accidental is proved by the cases in which the epileptic phenomena, mostly of the sensory jacksonian type, were confined to the heterolateral half of the body, as in my cases 1 and 2. I may cite Barkman,[109] Sainton and Baufle,[110] Walsh [37] (his case 2), Donley [94] and Diller.[13] In some cases signs of involvement of the pyramidal tract have been found on the contralateral side of the body (Bernstein,[11] Jumentié and Krebs [111] and MacBride [99]). Such signs, though mild, could be demonstrated on the contralateral side in cases 1, 2 and 3 of the present series. Merritt, Faber and Bruch [100] and Thiel [105] found cerebral calcification. The involvement of the homolateral hemisphere in cases of hemiatrophy, as shown

85. Mollaret, P.: Contribution à l'étude clinique et histologique de l'hémiatrophie faciale progressive, Rev. neurol. **2**:463, 1932.

86. Reiss: Hemiatrophia facialis progressiva, München. med. Wchnschr. **63**:1331, 1916.

87. Salus, F.: Beginnende Hemiatrophia facialis progressiva, Zentralbl. f. Haut- u. Geschlechtskr. **33**: 777, 1930.

88. Souques and Bourguignon: Un cas d'hémiatrophie progressive de la face amélioré par l'ionisation calcique, Rev. neurol. **29**: 204, 1922.

89. Wolff, H. G.: Progressive Facial Hemiatrophy, J. Nerv. & Ment. Dis. **69**:140, 1929.

90. Bost, C.: Progressive Facial Hemiatrophy, Arch. Pediat. **44**:497, 1927.

91. Bragman, L. J.: Progressive Facial Hemiatrophy: An Early Case, Arch. Pediat. **52**: 686, 1935.

92. Cited by Marburg.[42]

93. Černi, L.: Two Cases of Hemiatrophia unilateralis totalis, Sovrem. psikhonevrol., vol. 3, p. 494, 1926.

94. Donley, D. E.: Facial Atrophy Associated with Epilepsy, J. Nerv. & Ment. Dis. **82**:33, 1935.

95. Emminghaus, H.: Ueber halbseitige Gesichtsatrophie, Deutsches Arch. f. klin. Med. **11**:96, 1873.

96. Kiely, C. E.: A Case of Facial Hemiatrophy with Convulsions, J. Nerv. & Ment. Dis. **58**:229, 1923.

97. Kopczynski: Hemiatrophia faciei progressiva, Neurol. Centralbl. **28**:778, 1909.

98. Lande, L.: Essai sur l'aplasie lamineuse progressive, Thesis, Paris, no. 278, 1869.

99. MacBride, H. J.: Case of Facial Hemiatrophy, Brain **48**:133, 1925.

100. Merritt, K. K.; Faber, H. K., and Bruch, H.: Progressive Facial Hemiatrophy, J. Pediat. **10**:374, 1937.

101. Meyer, M.: Ein Fall von fortschreitender linksseitiger Gesichtsabmagerung, Berl. klin. Wchnschr. 7:23, 1870.

102. Meyer, O. B.: Lipodystrophia progressiva, München. med. Wchnschr. **66**:253, 1919.

103. Neustaedter, M.: A Case of Facial Hemiatrophy, M. Rec. **85**: 700, 1914.

104. Schultze: Hemiatrophia faciei, Deutsche med. Wchnschr. **40**:1290, 1914.

105. Thiel, R.: Roentgendiagnostik des Schädels bei Erkrankungen des Auges, Berlin, Julius Springer, 1932, case 2, figs. 44-47.

106. Zeller: Fall von rechtsseitiger Hemiatrophia facialis, Neurol. Centralbl. **2**:119, 1883.

107. Josefowitsch, cited by Ehrmann and Brünauer.[51]

108. Pollock, L. J.: Progressive Facial Hemiatrophy, Arch. Neurol. & Psychiat. **33**:888 (April) 1935.

109. Barkman, A.: Ein Fall von Hemiatrophia faciei progressiva mit epileptischen Anfällen, Deutsche Ztschr. f. Nervenh. **75**:1, 1922.

110. Sainton, P., and Baufle: L'hémiatrophie faciale, Gaz. de hôp. **83**:1841, 1910.

111. Jumentié, J., and Krebs, E.: Un cas d'hémiatrophie faciale progressive gauche avec hémiparésie et crises d'épilepsie bravais-jacksonienne du côté droit. Rev. neurol. **26**:117, 1913.

by Brain,[112] is of great significance. He reported a case "in which left facial hemiatrophy was associated with right-sided epilepsy, hemiplegia, hemianaesthesia, hemianopia and aphasia." The encephalogram showed marked dilatation of the ventricle on the left side and atrophy of the left hemisphere. The involvement of the homolateral hemisphere of the brain in cases of hemiatrophy, proved by clinical, pathologic and roentgenographic examinations, excludes mere coincidence. Generally speaking, the intimate ontogenetic relations between skin and brain make their simultaneous involvement understandable. Reference may be made to the vast and diversified group of congenital neuroectodermal dysplasias, especially to the common association of facial and intracranial hemangiomas.

CARDINAL SYMPTOM OF PROGRESSIVE FACIAL HEMIATROPHY

Cerebral involvement usually constitutes the last link in the chain of the extremely diversified symptoms of facial hemiatrophy. The disease presents such an immense variety of pathologic phenomena that they could hardly all be the direct result of a single lesion, wherever it may be and however intensive or extensive. The pathologic phenomena observed in some cases may be of indirect or secondary nature, and not invariably immediately or directly connected with the primary lesion.

Thus, especially with regard to the late cerebral manifestations, the questions arise: What are the primary, essential symptoms of hemiatrophy? What is on the "must list" of its symptoms? It is the fat and subcutaneous tissues which are primarily, and sometimes exclusively, affected. There is no case of hemiatrophy in which they are not involved. In some cases, of course, many other structures are also affected. But the starting point, at which the disease may stop, is the atrophy of fat and subcutaneous tissues. For instance, in the cases of Pichler,[113] Recht [114] and Strasburger,[115] in which the disease certainly was facial hemiatrophy, only unilateral atrophy of the fat of the cheek was present. In many a case the atrophy of the fat and subcutaneous tissues is so predominant as to be nearly exclusive (Calmette and Pagès [116]). Many authors have emphasized that the skin was completely intact (Cox and Maclure,[36] Donley,[94] Grünmandel,[117] Hoeflmayer,[118] Hoffmann, [119] Jendrassik,[14] Krüger,[120] Lauerbach,[43] Léri,[17] Luxenburger,[121] La Maire,[122] Stief [78] and Werba [123]) or little affected (Levkovski [124] and Smirnitski [125]). In some of my own cases the skin was only mildly affected or not at all. Even histologically, the skin in case 2 was normal. Changes in the skin may or may not follow atrophy of the fat and subcutaneous tissues. If they follow it, they may occur late in the disease. The predominant or exclusive involvement of the subcutaneous tissues induced Bitot and his pupil Lande,[98] in 1869, to call the disease *aplasie lamineuse progressive,* or *atrophie du tissu connectif,* and to regard it as *une affection propre, spéciale antopathique et protopathique de l'élément lamineux.* Neither the trigeminus nerve nor the cervical sympathetic chain is necessarily involved in cases of hemiatrophy. Many authors have stressed explicitly that no symptoms referable to the trigeminal nerve or the sympathetic nervous system could be observed (Cox and Maclure,[36] Hoeflmayer,[118] Kopczynski,[97] Salomon,[126] Stier [127] and Vazquez Rodriguez [128]). Lange (cited by Smirnitski [125]) found in a series of 163 cases only 18 in which there were sympathetic disturbances. In most of my own cases

112. Brain, R.: Diseases of the Nervous System, ed. 2, London, Oxford University Press, 1940, p. 599.

113. Pichler, K.: Einseitiger Schwund des Wangenfett-Propfes, Deutsche Ztschr. f. Nervenh. **61**:181, 1918.

114. Recht, G.: Zur Kasuistik des halbseitigen Wangenfettschwundes, Deutsche Ztschr. f. Nervenh. **134**:237, 1934.

115. Strasburger, J.: Ueber umschriebenen Fettgewebschwund des Gesichts, Med. Klin. **26**: 981, 1908.

116. Calmette and Pagès: Un cas d'hémiatrophie faciale progressive, Nouv. iconog. de la Salpêtrière **16**:26, 1903.

117. Grünmandel, S.: Hemiatrophia facialis incompleta, Zentralbl. f. Haut- u. Geschlechtskr. **18**:753, 1926.

118. Hoeflmayer, L.: Ein Fall von halbseitigem Gesichtsschwund, München. med. Wchnschr. **45**:391, 1898.

119. Hoffmann, A.: Zur Kenntnis der Hemiatrophia faciei progressiva, Neurol. Centralbl. **19**:999, 1900.

120. Krüger, H.: Ein Fall von Hemiatrophia faciei progressiva mit Sensibilitätsstörungen und gleichseitigen tonisch-klonischen Kaumuskelkrämpfen, Neurol. Centralbl. **35**:17, 1916.

121. Luxenburger, A.: Ueber zwei Fälle von Hemiatrophia facialis progressiva, München. med. Wchnschr. **48**:1413, 1901.

122. Le Maire, M.: A Case of Facial Atrophy, abstracted, Neurol. Centralbl. **17**:509, 1898.

123. Werba, D. H.: Hemiatrophy of the Face, M. Bull. Vet. Admin. **17**:291, 1941.

124. Levkovski, A. M.: Unilateral Progressive Atrophy of the Face, Obozr. psikhiat., nevrol. **7**:401, 1902.

125. Smirnitski, I. N.: Pathogenesis of Hemiatrophia Faciei, Zhur. nevropat. i psikhiat. **22**:599, 1929.

126. Salomon, S.: Ein Fall von Hemiatrophia progressiva mit Augennervensymptomen, Neurol. Centralbl. **26**:614 and 846, 1907.

127. Stier, E.: Ueber Hemiatrophie und Hemihypertrophie nebst einigen Bemerkungen über ihre laterale Lokalisation, Deutsche Ztschr. f. Nervenh **44**: 21, 1912.

128. Vazquez Rodriguez, A.: Un caso di hemitrofia facial, Pediatria espań. **16**:135, 1927.

there was no involvement of the trigeminus nerve or of the sympathetic system—except, of course, the trophic function of the latter. Therefore, the atrophy of the fat and subcutaneous tissues must be regarded as the primary and leading symptom of facial hemiatrophy.

EXTRAFACIAL EXTENSION OF THE ATROPHY

The involvement of the fat and subcutaneous tissues is by no means restricted to the face, as might be implied from the term "facialis." Since the atrophy primarily affects the frontal part of the head, the term "hemiatrophia frontalis progressiva" would be more appropriate. In many instances the atrophy has transgressed the boundary of the face. Saenger [129] stressed the involvement of the area of the nervus auricularis magnus and the nervus occipitalis minor. Oppenheim [29] and Fischer [61] found the upper triangle of the neck to be the starting point of the atrophic process. Archambault and Fromm [1] found that the process had initially developed in the domain of the second and third cervical roots. Stief [78] reported the extension of the atrophy to the shoulder. Several authors observed involvement of the homolateral arm (Bouveyron,[130] Collins,[131] Debray [131] and Vassilevski [25]). Remarkable are the cases of abortive involvement of the trunk homolaterally. Thus, Leskowski [93] found an atrophic strip similar to that of the face in the intercostal space between the eighth and the ninth rib. Extrafacial atrophic spots on the trunk were observed by Brunner,[92] Jendrassik [14] and Soltmann.[92] Several authors (Bernstein,[11] Heinemann [132] and Martin [133]) observed atrophy of the breast homolaterally. Raymond and Sicard [76] distinguished a definite type of hemiatrophy, "typus hemi-facio-scapulo-humero-thoracicus," several forms of which were found by Sternberg,[134] Virchow [135] and Wahl and Christian.[136] In a postmortem examination, Harbitz [137] observed that the kidney on the affected side was hypoplastic. Stief [78] found atrophy of the internal organs homolaterally, including the vocal cord, kidney, adrenal gland and ovary. Finally, cases in which complete hemiatrophy affected one half of the entire body have been observed. In addition to the cases mentioned by Archambault and Fromm,[1] the cases of the following authors may be cited: Collins,[131] Černi,[93] Chasanow,[46] Finesilver and Rosow,[138] Henschen,[73] Kroll,[47] Masten,[139] Nemlicher and Rappoport,[140] Orbison [68] and Vivado.[24] The case of Pelizaeus,[141] in which the hemiatrophy began in the left arm and extended to the left leg but spared the face and thorax, is unique. The atrophic process may even begin in the leg. According to Wilson,[142] a patient of Campbell's had atrophy of the fat of the entire right foot, and even the bones seemed to have suffered some atrophy. Campbell attributed the condition to facial hemiatrophy. Savill (cited by Wilson [142]) established an even closer relationship in a case in which a similar condition was associated with definite facial hemiatrophy. The involvement of other parts of the body, that is, on the same side as the facial atrophy, often may be not only abortive and minimal but latent, and therefore is frequently overlooked. In the case of Stief,[78] in which only the shoulder was involved, marked diminution of the sweat secretion was found homolaterally with Minor's test. Examples of every possible extension of hemiatrophy are reported in the literature, ranging from the initial form, in which only the forehead is affected, to complete involvement of one half of the body.

IRRITATIVE PHENOMENA ASSOCIATED WITH PROGRESSIVE FACIAL HEMIATROPHY

The physiopathologic process that leads to hemiatrophy must be an active one, a surplus of innervation which brings about destruction of

129. Saenger: Hemiatrophia faciei, Neurol. Centralbl. **31**:607, 1912.

130. Bouveyron: De l'hémiatrophie faciale dans ses rapports avec les lésions du ganglion cervical inférieur, Rev. neurol. **10**:211, 1902.

131. Cited by Cassirer and Hirschfeld, in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1935, vol. 17, p. 246.

132. Heinemann, W.: Ueber Hemiatrophia faciei, Inaug. Dissert, Leipzig, B. Georgi, 1907.

133. Martin, J. P.: A Case of Facial Hemiatrophy with Lack of Development of the Breast on the Same Side, Brain **48**:140, 1925.

134. Sternberg: Ueber eine besondere Form der Hemiatrophia faciei, Arch. f. Psychiat. **99**:815, 1933.

135. Virchow: Ueber neurotische Atrophie, Berl. klin. Wchnschr. **17**:409, 1880.

136. Wahl, W., and Christian, P.: Ueber einen Fall von idiopathischer Hemiatrophia humero-scapulothoracalis mit anämischen und telangiektatischen Naevi und Irisheterochromie, Deutsche Ztschr. f. Nervenh. **144**:1, 1937.

137. Harbitz: Akromegalie und Hemiatrophia facialis progressiva, Zentralbl. f. allg. Path. u. path. Anat. **22**:801, 1911.

138. Finesilver, B., and Rosow, H. M.: Total Hemiatrophy, J. A. M. A. **110**:366 (Jan. 29) 1938.

139. Masten, M. G.: Asymmetry: Unilateral Atrophy and Facial Hypertrophy, Arch. Neurol. & Psychiat. **35**:136 (Jan.) 1936.

140. Nemlicher, L. J., and Rappoport, B. J.: Hemiatrophy of Face and Body Combined wth Idiopathic Dermatologic Processes, Vrach. delo **8**:278, 1925.

141. Pelizaeus: Ueber einen ungewöhnlichen Fall von progressiver Hemiatrophie, Neurol. Centralbl. **16**: 530, 1897.

142. Wilson, S. A. K.: Neurology, edited by A. Ninian Bruce, Baltimore, William Wood & Company, 1940, vol. 2, p. 1049.

tissues. It is not merely hypotrophy or underdevelopment but an actual disintegration of tissue. Progressive facial hemiatrophy can be distinguished easily from facial asymmetry, congenital hypotrophy or hypotrophy due to disease, such as cerebral palsy in children, facial paralysis, poliomyelitis pontis or torticollis. In these conditions there is simply a retardation in growth, a minus of activity, whereas in hemiatrophy a plus of activity and an increase of reflexive activity seem to be prevalent.

Since the trophism of the fat and subcutaneous tissues is unquestionably under the influence of the sympathetic nervous system, facial hemiatrophy is a disorder in which the centers and tracts of the sympathetic system that are concerned with the metabolism of fat and of the subcutaneous tissues are essentially and primarily involved. Many authors have assumed that a pathologic state of irritation leads to facial hemiatrophy (Chasanow,[46] Goering [143] Müller,[144] Cassirer,[45] Stilling,[145] Kroll [47] and Brüning [146]). It is for this reason that periarterial sympathectomy was recommended for facial hemiatrophy. This operation was performed with some success, as reported by Brüning,[146] Forster,[131] Leriche [131] and Trepte.[147] From their pharmacodynamic tests, Marinesco, Kreindler and Façon [148] concluded that hemiatrophy was due to hyperfunction of the sympathetic nervous system. By using the epinephrine test of Muck and the sweating test of Minor, Joël [149] found in 4 cases irritative phenomena in the peripheral sympathetic system of the area involved. This does not exclude the possibility that, with this hyperfunction of the vegetative system, its hypofunction may coexist or develop later (Smirnitski [125]). Oppenheim [29] observed cases in which symptoms of paralysis and irritation of the sympathetic nervous system were present.

While the cardinal symptom of hemiatrophy, the atrophy of fat and subcutaneous tissues, indicates a state of irritation in the trophic sympathetic system, this state of irritation and hypertonus definitely extends over other functions of the sympathetic nervous system and may spread to the cranial and the spinal nerves. In the area affected by the hemiatrophy, phenomena of irritation predominate and often precede those of palsy. The following symptoms of sympathetic involvement may be present: mydriasis, exophthalmos, hyperhidrosis, heterochromia of the iris (as in my case 1), conjunctival injection (Hughes [150] and Werba [123])—with similar findings in case 5 of this series—rhinorrhea, nevi, pigmentation, vitiligo, alopecia, blanching of the hair, scleroderma, *mal perforant* and Raynaud's disease. The secretion of sweat and sebum is often increased at first and decreased later. On microscopic examination of the capillaries, Pollak [151] found signs of a "spastic-atonic vasoneurosis." Signs indicating a state of irritation in the cranial nerves have often been observed. They include spasm of the muscles innervated by the facial and trigeminal nerves (Courtet,[152] Hoeflmayer,[118] Jendrassik,[14] Krüger,[120] Nemlicher and Rappoport,[140] Sachs,[153] Vivado [24] and Wirschutzki [154]). Neuralgia in the trigeminal area is common; it begins early; in fact, it is often a precursor of the disease. In the area of the fifth nerve such manifestations as hyperesthesia, tender Valleix pressure points, paresthesia and homolateral hyperesthesia for taste are sometimes observed.

A local disturbance in the metabolism of fat has been considered here as a primary and cardinal feature of hemiatrophy. The peripheral apparatus in charge of the trophism of fat and subcutaneous tissues is evidently in such a state of increased, uncontrolled, unregulated activity that it leads to increased disintegration of tissues and subsequently to atrophy. The trophic influences for the face are not transmitted through the facial nerve but are mediated by the sensory fibers of the trigeminus nerve. However, these fibers do not belong primarily to the trigeminus but are derived from the cervical sympathetic trunk. Thus, the trophic stimulus passes from the sympathetic fibers to the trigeminal nerve in order to reach the tissues. It is easy to under-

143. Goering, D.: Ueber den Einfluss des Nervensystems auf das Fettgewebe, Ztschr. f. Konstitutionslehre **8**:312, 1922.

144. Müller, L. R.: Lebensnerven und Lebenstriebe, Berlin, Julius Springer, 1931; Ueber den Einfluss des Nervensystems auf das Fettgewebe, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **33**:428, 1921.

145. Stilling: Untersuchungen über die Spinal-Irritation, Leipzig, O. Wigand, 1840, p. 325.

146. Brüning, F.: Die tropische Funktion der sympathischen Nerven, Klin. Wchnschr. **2**:67, 1923.

147. Trepte, G.: Hemiatrophia totalis mit Sclerodermie und Sympathicusoperation, Ztschr. f. d. ges. Neurol. u. Psychiat. **124**:809, 1930.

148. Marinesco, Kreindler and Façon: Sur la pathologie de l'hémiatrophie faciale, Paris méd. **13**:269, 1932.

149. Joël, W.: Ueber Hemiatrophia faciei progressiva, Inaug. Dissert., Berlin, 1932.

150. Hughes, W. N.: Progressive Facial Hemiatrophy, J. Nerv. & Ment. Dis. **84**:683, 1936.

151. Pollak, F.: Ein eigenartiger Fall von einseitiger Hemiatrophie und seine Beziehungen zum vegetativen Nervensystem, Arch. f. Dermat. u. Syph. **159**:188, 1930.

152. Courtet: Atrophie unilatérale de la face, Gaz. hebd. de méd. **13**:196, 1876.

153. Sachs, B.: Progressive Facial Hemiatrophy with Some Unusual Symptoms, M. Rec. **37**:292, 1890.

154. Wirschutzki: Zur Kasuistik der Hemiatrophia facialis progressiva, abstracted, Neurol. Centralbl. **25**: 1008, 1906.

stand that a state of irritation in one of the manifold conductive systems of the trigeminal nerve may be easily transmitted to the other systems which pass through the same nerve. The irritation jumps over to a neighboring tract and sets up irritative phenomena. Other examples of transmission of irritation from one system to another when the systems are conveyed over the same nerve may be cited. Cassirer [45] stated that the most common cause of trophic disturbances is irritation which comes from the sensory tract and is transmitted to the sympathetic nervous system. Unilateral trophic changes occur in the face in cases of long-standing trigeminal neuralgia (Surat [155]). Facial spasm is seen in association with trigeminal neuralgia. Thus it is conceivable that in cases of hemiatrophy irritation in the trophic centers and tracts is transmitted to other tracts of the sympathetic nervous system and to the sensory and motor tracts. A similar mechanism underlies the phenomena of Head's zones. The trophic tracts of the face pass through the cervical sympathetic system and the trigeminus; thus, a concomitant irritation of other vegetative, sensory or motor tracts of the face is possible.

INFLAMMATORY PROCESSES IN THE AREA OF ATROPHY

Not only irritative phenomena but inflammatory processes occur in the tissues of the atrophic area. These processes may differ widely in location and character. They include neuritis of the facial nerve (Gowers [156]) or of the trigeminal nerve (Mendel,[66] Loebl and Wiesel [157]), herpes (Hoeflmayer [118] and Trotter [158]) and inflammation of the cervical sympathetic ganglia (Brüning [146] and Kroll [47]). Especially common are inflammatory processes involving the eye on the affected side: keratitis neuroparalytica, ulcers, iritis, iridocyclitis, choroiditis, cataract and edema of the papilla (Beer,[62] Chaillous and Thibierge,[159] Emminghaus,[95] Flint,[31] Graff,[160] Mollaret,[85] Morelli,[161] Neustaedter,[103] Stief,[78] Weekers [162] and Wolfe and Weber.[28]). Lauber [16] found tuberculosis of the eye on the affected side. In case 2 of the present series the homolateral eye showed tuberculous infection very early. Involvement of the lymph glands of the neck was observed by Loewy-Hattendorf,[18] Oppenheim [29] and Siebert.[163] Numerous observations of homolateral implication of the lungs and pleura were made. Archambault and Fromm [1] noted the presence of pulmonary tuberculosis in a strikingly large percentage of cases. The following reports may be cited: Barrel,[164] Bouveyron,[130] Černi,[93] Loewy-Hattendorf,[18] Souques,[165] Steven [166] and Weinberg and Hirsch.[167] In a case of hemiatrophy of the face, trunk and extremities, the last-mentioned authors found ulcerations of the affected arm and leg.

Numerous investigations have been made concerning the influence of the sympathetic nervous system on the permeability of the vessels and on inflammation. Cannon [168] showed that "smooth muscle, whether normally stimulated by parasympathetic influences or stimulated or inhibited by sympathetic influences, is rendered more excitable to chemical agents by destruction of the ultimate innervating neurones." Recent experiments of Asher [169] demonstrated this influence of the sympathetic system:

> If on one side the cervical sympathetic is cut and both eyes are exposed to the rays of a quartz lamp of the same intensity and duration, either only the cornea of the side without sympathetic shows lesions, or, if both corneas have been affected, on the side without sympathetic the lesions are more severe and take longer to heal.[169a]

Orr and Sturrock [170] studied experimentally the

155. Surat, W. S.: Ueber einseitige Störung der Gesichtstrophik, Monatschr. f. Psychiat. u. Neurol. **77**: 202, 1930.

156. Gowers, W. R.: The Influence of Facial Hemiatrophy on the Facial and Other Nerves, Rev. Neurol. & Psychiat. **4**:1, 1906.

157. Loebl, H., and Wiesel, J.: Zur Klinik und Anatomie der Hemiatrophia facialis progressiva, Deutsche Ztschr. f. Nervenh. **27**:355, 1904.

158. Trotter, W.: Recurrent Herpes Zoster of the Face with Hemiatrophy, Proc. Roy. Soc. Med. (Sect. Dermat.) **4**:43, 1915-1916.

159. Chaillous and Thibierge: Iritis chez une malade atteinte d'hémiatrophie de la face, Arch. d'opht. **43**:55, 1926.

160. Graff, H.: Ein Fall von Hemiatrophia facialis progressiva verbunden mit neuroparalytischer Ophthalmie, Inaug. Dissert., Dorpat, H. Laakmann, 1886.

161. Morelli: Dystrofie et trofoneurose, Gazz. d. osp. **2**:1528, 1905.

162. Weekers: Hemiatrophie faciale, Rev. neurol. **28**:1154, 1921.

163. Siebert, H.: Ein Fall von rechtsseitiger Gesichtsmissbildung mit Erscheinungen der Hemiatrophia faciei, Deutsche Ztschr. f. Nervenh. **56**:320, 1917.

164. Barrel, E.: De l'hémiatrophie faciale, Thesis, Lyon, no. 132, 1902.

165. Souques: Syndrome oculo-papillaire, Bull. et mém. Soc. méd. d. hôp. de Paris **19**:484, 1902.

166. Steven, J. L.: Case of Scleroderma, Glasgow M. J. **50**:401, 1896.

167. Weinberg, F., and Hirsch, F.: Hemiatrophia facialis progressiva bei chronischen Lungenaffektionen, etc., Deutsche Ztschr. f. Nervenh. **66**:205, 1920.

168. Cannon, W. B.: A Law of Denervation, Am. J. M. Sc. **198**:737, 1939.

169. Asher, L.: (*a*) Report on the Mode of Action of the Sympathetic and Its Integrative Function, abstracted, International Neurological Congress, London, 1935, p. 37; (*b*) Trophic Function of the Sympathetic Nervous System, J. A. M. A. **108**:720 (Feb. 27) 1937.

170. Orr, D., and Sturrock, A. C.: Toxi-Infective Lesions in the Central Nervous System, Lancet **2**:267, 1922.

lesions found when after division of the cervical sympathetic trunk general intoxication had been produced. Their conclusion was that "the sympathetic nervous system is an important factor in the localization of lesions, not only in the central nervous system but probably wherever they may occur." The influence of the sympathetic nervous system on the pial vessels has been shown conclusively in the experiments of Forbes and Wolff,[171] who used the method of direct inspection through a skull "window." A definite contraction of the pial arteries could be seen on excitation of the cervical sympathetic trunk. On stimulation of the cervical sympathetic chain in unanesthetized cats, Thomas [172] found slight constriction of the ipsilateral pial arterioles. The histopathologic changes found by Stief [75] in a case of facial hemiatrophy showed conclusively the influence of the cervical sympathetic fibers on the vasomotor regulation of the cerebral vessels.

Every tissue deprived of its normal sympathetic innervation provides an area of predilection for infection. Since the vessels of the pia are under sympathetic control, any disturbance of this control renders the corresponding area of the brain more susceptible to toxi-infections. If any toxic or infective process is present in the body, coexistent with facial hemiatrophy, the entire area affected by the hemiatrophy (usually the area of the cervical sympathetic chain, which unilaterally supplies the brain, the head and the area of the upper thoracic segments) is the site of predilection for localization of this process. The infection spreads abundantly in the soil prepared by the derangement of the sympathetic innervation. The affected area yields easily, since it is a locus minoris resistentiae. The inflammatory processes which accompany hemiatrophy and are located in the entire affected area can be thus easily explained. This area includes the brain, which in its homolateral half shows a predilection for encephalitic processes. In case 2, such an encephalitic process was demonstrated histologically. The various pathologic conditions which affect the homolateral half of the brain in cases of facial hemiatrophy can be explained on the basis of disturbed innervation.

Conclusion.—It is not the inflammatory or other processes in the area of the cervical sympathetic chain which produce hemiatrophy; it is the reverse; the hemiatrophy is the primary process, which, by weakening the resistance of the affected tissues, makes them the playground for toxi-infections of any kind from anywhere.

171. Forbes, H. S., and Wolff, H. G.: Cerebral Circulation: III. The Vasomotor Control of Cerebral Vessels, Arch. Neurol. & Psychiat. **19**:1057 (June) 1928.

172. Thomas, C. B.: Constriction of Pial Vessels Produced by Stimulation of the Cervical Sympathetic Chain, Am. J. Physiol. **114**:278, 1936.

CENTRAL ORIGIN OF PROGRESSIVE FACIAL HEMIATROPHY

In order to explain the pathogenesis of hemiatrophy, the existence of a pathologic process has been assumed in the corresponding portion of the sympathetic nervous system which leads to its increased and uncontrolled activity. When this irritation is transmitted to neighboring tracts and centers, it may eventually lead to their paralysis. Since the face is most commonly the seat of the atrophy, the cervical sympathetic trunk must be involved. The question arises whether or not this structure is primarily involved. The fact that inflammatory or traumatic lesions of the cervical sympathetic chain are unable to produce facial hemiatrophy speaks against primary involvement. The case of Seeligmüller [173] which supposedly demonstrated the development of hemiatrophy after injury of the cervical sympathetic trunk, was certainly "not a case of facial hemiatrophy" (Möbius [41]). According to statistics gathered by Kaelin,[174] the cervical sympathetic system was injured in 12 of 1,196 thyroidectomies, but in none of the cases did facial hemiatrophy develop. Naffziger [175] has never seen hemiatrophy after injury to the cervical sympathetic system. It would be difficult to believe that any inflammatory process of the sympathetic nervous system could produce facial hemiatrophy, with its extremely chronic course and its tendency to remain stationary for years, or even decades. The numerous cases of hemiatrophy with only trophic lesions could not be explained on this basis. It had to be assumed that for many years the inflammatory process selects only the trophic mechanism inside the cervical sympathetic chain and spares all others. Patients with hemiatrophy usually show no signs of an inflammatory process in the cervical sympathetic chain. When the extremely insidious beginning and the slow development of the disease are considered, an inflammatory origin appears still more improbable. It may be men-

173. Seeligmüller, A.: Ein Fall von akuter traumatischer Reizung des Halssympathicus, Arch. f. Psychiat. **5**:835, 1875.

174. Kaelin, W.: Ueber Störungen von Seiten des Halssympaticus bei einfacher Struma und im Anschluss an deren operative Behandlung, Leipzig, F. C. W. Vogel, 1915.

175. Naffziger: Personal communication to the author.

tioned that in cases of Trepte [147] and Grabs [176] histologic examination of the cervical sympathetic fibers extirpated surgically showed normal tissue. With use of the epinephrine test of Muck and the sweating test of Minor, Joël [149] was unable to demonstrate in 4 cases any peripheral causation of the existing irritative phenomena in the sympathetic nervous system.

The increased tonus and the state of irritation in the sympatheic trophic centers and tracts in the area of the hemiatrophy need not be explained on the basis of a direct and primary local irritation of the periphery. If lack of inhibition due to loss of control by higher centers is assumed, the primary lesion would lie in the highest centers that regulate the nutrition of the tissues. A disturbance of these centers would produce an inhibited, and therefore increased, reflex activity of the lower trophic centers and consequently would lead to atrophic changes in the tissues. This situation would be analogous to that found in the pyramidal and extrapyramidal motor systems, in which higher situated lesions produce increased reflex activity in the lower parts. Thus conceived, facial hemiatrophy would represent, so to say, a spastic paralysis of the lower trophic centers due to involvement of the higher ones.

Certain autonomic phenomena observed with lesions of the central nervous system can best be explained in this way. For instance, Kinnier Wilson regarded as a release phenomenon the profuse sweating of the feet and legs which sometimes is seen with tumors of the spinal cord. Kerr and Noble's [177] sign of increased tension of the skin below the level of a tumor of the cord, which indicates hypertonus, may best be explained as such a release phenomenon. Cannon [168] tried to apply to the autonomic nervous system Hughlings Jackson's theory of a hierarchy of functions in the central nervous system and his ideas of increased activity of the lower levels due to loss of control of the higher ones.

The present status of knowledge of the trophic influence of the nervous system (Asher,[169] Fleischhacker,[178] Goering,[143] Müller [144] and Pollak [179]) allows the assumption that high trophic centers exist in the brain, especially in the hypothalamus. Disturbances of the metabolism of fat, particularly those of hemilateral distribution (Kroll [47] and Lange [180]) observed after encephalitis epidemica, have given support to the theory of the trophic control exerted by cerebral centers. To these high cerebral centers are subordinated other centers located deeper—in the brain stem, the medulla and the spinal cord and at the periphery. A lesion at any link in this chain can produce an imbalance of the whole closely organized system of subordinated centers, an imbalance which would increase in direct proportion to the level of the lesion. According to the character, progress, extension and location of the lesion and to the status of the lower centers affected, the pathologic process set forth in the tissues may at any time come to a standstill because the lower centers may have adapted themselves to the new situation. This readjustment of the lower centers may account for the abortive and stationary forms.

Which of the numerous centers regulating nutrition of the tissues are affected in hemiatrophy? For many reasons, involvement of the highest centers of the cerebrum must be assumed. Of course, such an involvement is present in cases in which there is complete or incomplete atrophy of one half of the body. The fact might be stressed that in many cases of hemiatrophy in which apparently only the face is affected, signs of abortive involvement of other parts of the body on the same side are observed.

It is especially the concomitant features of hemiatrophy which seem to indicate cerebral involvement, the progressive facial hemiatrophy being merely a part of the general autonomic imbalance which has resulted from deranged central trophic control. Wolff and Ehrenclou [181] reported a case in which the facial hemiatrophy was combined with a disturbance of fat metabolism (lipodystrophy), a perversion of sensation, apparently of thalamic origin, and a peculiar affective state. Miskolczy and Dancz [182] reported a case of postencephalitic hemiparkinsonism combined with total hemiatrophy of the same side. In a case reported by Kirschenberg [183] hemiatrophy was accompanied homolaterally with

176. Grabs: Fall von Hemiatrophia faciei progressiva, Neurol. Centralbl. **33**:84, 1914.

177. Kerr, W. J., and Noble, C. A., Jr.: New Sign Found in Transverse Lesions of Spinal Cord, California & West. Med. **45**:346, 1936.

178. Fleischhacker, H.: Die trophischen Einflüsse des Nervensystems, in Bethe, A.; von Bergmann, G., and others: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1927, vol. 10.

179. Pollak, F.: Zur Frage der cerebralen Trophik, Arch. f. Psychiat. **89**:788, 1930.

180. Lange, W.: Wachstumsstörungen bei chronischer Encephalitis epidemica, Allg. Ztschr. f. Psychiat. **97**: 135, 1932.

181. Wolff, H. G., and Ehrenclou, A. H.: Trophic Disorders of Central Origin, J. A. M. A. **88**:991 (March 26) 1927.

182. Miskolczy, D., and Dancz, M.: Hemiatrophie mit Hemiparkinsonismus, Deutsche Ztschr. f. Nervenh. **127**:194, 1932.

183. Kirschenberg, E.: Zur Frage der Hemiatrophia faciei progressiva mit zentraler Genese, Folia neuropath. Estoniana **3-5**:94, 1925-1926.

hypalgesia, hyperesthesia for cold and hyperhidrosis. The combination of hemiatrophy with the Argyll Robertson pupil (Langelaan [184] and Surat [155]), anisocoria (Wolff [89]), acromegalic features (Wolff [89]), exophthalmos (Meyer [19]), extrapyramidal phenomena (Recht [114]), apoplexy and thalamic pain (Süss [185]) point to a central origin. A combination of hemiatrophy and homolateral hemitetany was reported by Hanse.[186] In the case of Léri [17] there was on the same side paralysis of the third to the twelfth cranial nerve, which led him to assume the presence of chronic polioencephalitis with a mesencephalic lesion of the sympathetic nervous system. Faber [187] reported that three diseases—hemiatrophy, vitiligo and myxedema—appeared in succession in the same case; he supported the view that all three disturbances were due to "an interference with the functioning of the vegetative centers in the midbrain." Cases in which the hemiatrophy is of alternating type (Bernstein,[11] Lunz,[188] Ratner [20] and Volhard [189]) clearly point to a central origin. The alopecia seen in cases of hemiatrophy can thus be easily explained (Stepp [190] and Ratner [191]). Lauerbach,[43] Mankowski,[192] Pollak,[179] Vassilevski,[23] Vivado [24] and others assumed the presence of a central lesion in cases of hemiatrophy. Its appearance after encephalitis epidemica with or without other vegetative disturbances of hemiplegic type (Kroll,[47] Mankowski,[192] Meyer,[19] Recht [114] and others) is in this respect remarkable. From his pharmacodynamic studies on patients with hemiatrophy, Bini [89] concluded that a central lesion was a more likely cause than a lesion of the cervical sympathetic trunk. Asymmetric responses from the halves of the body in pharmacologic experiments were noted by Donley,[94] Finesilver and Rosow [138] and Marinesco and associates.[148] Histologic examination in 1 case led Stief [78] to attribute hemiatrophy to disease of the opposite half of the hypothalamus.

Thus, one may conceive that hemiatrophy belongs to the release phenomena due to lack of inhibition and of normal regulation on the part of the highest trophic centers, with the consequent hypertonic and dystonic disturbances in the peripheral sympathetic trophic system.

PROGRESSIVE FACIAL ATROPHY—A HEREDODEGENERATION

What is the nature of the primary disturbance of the highest trophic centers? Many facts indicate that it might be a pathologic condition which belongs to the vast group of developmental defects so abundant in neurology. Many names have been coined to characterize this group of chronic endogenous, autochthonous, systemic degenerations. Oppenheim spoke of congenital inferiority; Ziehen, of nuclear aplasias and dysplasias; Bing, of wearing out of a congenitally inferior system; Adler, of a congenital short span of life of single parts of the nervous system; Gowers, of abiotrophy, and Jendrassik, of heredodegeneration. Hemiatrophy may be such a heredodegeneration; it is a developmental trophic defect, a "neuronic decay," to use the expression of Kinnier Wilson's.

The course of hemiatrophy is the same as that of all other heredodegenerations. It begins in preadolescence (the statistics of Beer [62] showed that in 75.2 per cent of 109 cases the defect began before the twentieth year) and without apparent cause; it develops slowly and later becomes stationary. Patients with hemiatrophy show more pathologic conditions in their ancestry than normal persons. Among these conditions are consanguinity, epilepsy (in the case cited by Bartels [193] an uncle and a grandmother of the patient were epileptic), psychic disturbances, developmental defects and stigmas of degeneration. The mother of a patient of Léri and Weill [194] had the Marcus Gunn phenomenon. Two brothers of the father of a patient of Wahl and Christian [136] suffered from muscular dystrophy. Thomas [195] mentioned a case of facial hemiatrophy in a family affected with Friedreich's disease. Cases of hereditary and familial hemiatrophy are on record.

184. Langelaan, J. W.: Un cas d'hémiatrophie faciale avec signe d'Argyll Robertson contralatéral, Rev. neurol. **26**:520, 1913.

185. Süss, A.: Ueber eine Form halbseitiger trophischer Störungen nach einem apoplektischen Insult, Inaug. Dissert., Munich, Bottrop i W., Postberg, 1938.

186. Hanse, A.: Ueber halbseitige vegetative Störungen, Deutsche Ztschr. f. Nervenh. **102**:162, 1928.

187. Faber, K.: Facial Hemiatrophy—Vitiligo—Myxoedema, Acta med. Scandinav. **5**:419, 1934.

188. Lunz, M. A.: Hemiatrophia totalis cruciata, Deutsche med. Wchnschr. **23**:185, 1897.

189. Volhard, F.: Ueber chronische Dystrophie und Trophoneurosen der Haut im Anschluss an kasuistische Mitteilungen; Fall von Hemiatrophia facialis progressiva mit gekreuzter Pigmentation, München. med. Wchnschr. **50**:1108, 1903.

190. Stepp, C. L.: Beitrag zur Beurteilung der nach heftigen Körpererschütterungen (bes. Eisenbahnunfällen) auftretenden Störungen, Deutsche med. Wchnschr. **15**:66, 1889.

191. Ratner, T.: Alopecia universalis und Nervensystem, Deutsche Ztschr. f. Nervenh. **104**:146, 1928.

192. Mankowski: Zur Pathogenese der Hemiatrophia facialis, Arch. f. Psychiat. **78**:572, 1926.

193. Bartels: Hemiatrophia faciei, Ztschr. f. Augenh. **66**:367, 1925.

194. Léri, A., and Weill, J.: Phénomène de Marcus Gunn congénital et héréditaire, Bull. et mém. Soc. méd. d. hôp. de Paris **45**:875, 1929.

195. Thomas, A.: Héredoatrophies cérébelleuses, cerebellifuges et cérébellipétes: III. Congrès Neurologique International, Comptes rendus des Séances, Copenhagen, 1939, p. 201.

In Seeligmüller's [173] case the mother's sister was affected; in Klingmann's [6] case the grandmother, mother and twin daughters had the disease; in Raymond and Sicard's [76] case the brother and sister were affected; in the cases reported by Geist,[196] Boenheim [80] and Reiss [86] other members of the family were affected, and in Meyer's [19] case the mother's sister had the disease. The association of hemiatrophy and epilepsy has been discussed. Hemiatrophy is often associated with other degenerative diseases of the nervous system, such as psychopathy (Chasanow,[46] Donley,[94] Flint,[31] Hübner,[197] Klingmann,[6] Merritt and associates,[100] Meyer,[19] Wahl and Christian,[136] and Wolfe and Weber [28]), neuropathy (Černi,[93] Boenheim,[80] Oppenheim [29] and Krüger [120]), imbecility and underdevelopment. Beer [62] stated that 27 per cent of all patients suffering from hemiatrophy are neurotic. Cassirer [45] spoke of general inferiority and instability of the vasomotor apparatus and of the whole nervous system in these patients. In patients with hemiatrophy outspoken signs of developmental defects in other organs, such as congenital palsy of the ocular muscles, congenital hemiatrophy of the tongue, congenital facial palsy and other inherited anomalies, are often seen (Ellerbrock [198] and Harbitz [137]). Remarkable is the association of hemiatrophy with congenital torticollis (Sorsby and Shaw [199]); gigantism, eunuchoidism and acromegaly (Boenheim [80]); defect of the pectoral muscle (Kroll [47] and Chasanow [46]); heterochromia of the iris (my case 1); telangiectatic and anemic nevi (Wahl and Christian [136]); linear nevus (Tobias,[200] Marinesco and associates [148]); an anomaly of the hair whorl (Berger [201]); supernumerary nipples (Boenheim [80]); degeneration of the retina (Bini [39]), and gynandromorphism (Wolfe and Weber [28]). Instances of nonsyphilitic fixed pupil were reported (Langelaan,[184] Noïca and Vicol,[202] Oppenheim,[29] Salomon [126] and others) in which the defect was considered by some investigators as congenital. My view, expressed in a previous paper,[2] that hemiatrophy belongs to the large group of developmental defects of the nervous system, was shared by Flint [31] in the discussion of 1 of his cases:

> The suggestion, therefore, is that a congenital or inherited nervous instability is at the root of this condition and the history of this case [constitutional psychic abnormalities in the patient, her sister and her mother] certainly strengthens that suggestion.

The fact that hemiatrophy occasionally makes its appearance late in life does not speak against its heredodegenerative character. In discussing a case of hemiatrophy, Möbius [41] argued that since the symptoms appeared only at the age of 37, the patient could not have had this disease. One can hardly subscribe to his view. Marburg [42] cited a number of cases of undeniable hemiatrophy in which the symptoms appeared after the age of 30. Archambault and Fromm [1] collected from the literature cases in which the symptoms developed at ages ranging from 28 to 74 years.

The hypothesis that hemiatrophy is a cerebral heredodegeneration is supported by the argument that no adequate and plausible external cause can be found for this disease—with its slow beginning; its slow, unremitting, relentless development, and its refractoriness to treatment. As is often the case with degenerative diseases of the nervous system, the patient, to whom the idea of a spontaneous degeneration of nervous tissue is inconceivable, seeks, and usually finds, an incident that must have caused the symptoms. He often unconsciously falsifies his memories, postdates the onset and stubbornly adheres to his story. Frequently he succeeds in inveigling the physician into believing his story. A careful survey of the literature shows that there is hardly a morbid condition that has not, at some time or other, been regarded as a cause of hemiatrophy. Among the agents considered to be factors are local trauma (in 25 per cent), local infections and operations, tonsillitis, angina, extraction of teeth, alveolar abscess, exposure to cold, abscess of the ear, otorrhea, pneumonia, the forced passage of a sound down the lacrimal duct, erysipelas of the face, removal of adenoids, application of ethyl chloride spray and burns. These trivial, and in many instances very common, factors can hardly be held responsible for the development of hemiatrophy, which is one of the rarest diseases known. Trauma of the brain also is mentioned as an etiologic factor. It is hardly conceivable that any trauma could set up a system of degeneration in the depths of the brain of the slow progressive character seen in hemiatrophy.

196. Geist: Ein Fall von halbseitiger Unterentwicklung, Neurol. Centralbl. **30**:122, 1911.

197. Hübner: Bilaterale Hemiatrophia faciei, Deutsche Ztschr. f. Nervenh. **65**:26, 1920.

198. Ellerbrock, N.: Einige interessante angeborene Missbildungen, Zentralbl. f. Gynäk. **46**:898, 1922.

199. Sorsby, A., and Shaw, M.: The Refraction in Cases of Congenital Torticollis Associated with Hemiatrophy of the Face, Brit. J. Ophth. **16**:222, 1932.

200. Tobias, N.: Extensive Linear Nevus with an Associated Hemiatrophy, Arch. Dermat. & Syph. **18**: 451 (Sept.) 1928.

201. Berger, O.: Ein Fall von Hemiatrophia facialis progressiva, Deutsches Arch. f. klin. Med. **22**:432, 1878.

202. Noïca, D., and Vicol, A.: Un cas d'hémiatrophie faciale droite, Bull. Soc. méd. hôp. de Bucarest **6**:96, 1924.

Although during World War I an enormous number of head injuries occurred, now, after twenty-six years, not a single record of subsequent hemiatrophy can be found in the literature. The extensive neurologic and neurosurgical literature on head injury does not contain a single report of hemiatrophy as a result of cerebral trauma. The salient point is that in the majority of cases no external cause whatsoever can be brought into relationship with the development of the disease. Only an endogenous lesion of slowly progressive character, such as heredodegeneration, would offer an explanation for the disease. However, if a congenital developmental defect exists, say in the diencephalon, severe trauma may carry its influence into the depth of the brain and thus may accelerate, or even initiate, the disease. However, only a predisposed brain could react in this manner; never a healthy one. Severe trauma may influence the deepest parts of the brain in cases of dystrophia adiposogenitalis and of diabetes insipidus. In the same manner, trauma may influence a heredodegenerative process. Oppenheim [29] observed that an injury to the head initiated an ophthalmoplegia which was based on a congenital maldevelopment.

The assumption that peripheral trauma may influence the process of hemiatrophy is compatible with the hypothesis that this disease is due to a centrally located heredodegeneration. In a few reported cases peripheral trauma was so closely connected with the hemiatrophy, as regards both time of onset and localization, that some connection between them has to be considered. Hoffmann,[119] for instance, reported the case of a 10 year old boy who, at the age of 6, fell with the right cheek against the edge of the pavement and received a wound over the right brow. At this area a pale spot developed several months later, and little by little the right half of the face showed retardation. One is confronted here with the same problem that is presented by the influence of peripheral trauma on the development of other heredodegenerations, such as paralysis agitans or amyotrophic lateral sclerosis. Many workers, among them Kinnier Wilson, observed the beginning of amyotrophic lateral sclerosis in an area which had undergone injury. What might be the explanation? The injury is, of course, not the cause of the pathologic process. There can hardly be such a *reaction à distance* from the periphery to the brain. But hemiatrophy, considered as a heredodegeneration, has a long "incubation period." The developmental defect in the trophic centers had existed a long time before the injury occurred. When the highest trophic centers fail, the lower ones may for some time adjust themselves to the new situation and may maintain normal nutrition of the tissues. The balance of the various trophic centers had been so delicately maintained that it just provided the right trophism for the so-called passive tissues, but only under favorable external conditions. The regulation of nutrition fails when higher requirements are put on these structures after trauma. In this way the appearance of hemiatrophy in puberty can be explained, during which time, owing to the growth of the body, higher requirements are put on the trophic apparatus. Every trauma or local infection also causes irritation of the sensory tracts. The stimulus is transmitted to the vegetative system and can bring about trophic disturbances. Similar conditions prevail, for instance, in the post-traumatic bone atrophy of Sudeck. In cases of hemiatrophy, when the higher regulation and inhibition is more or less defective, the trophism is more influenced by peripheral sensory stimulation. Thus, latent hemiatrophy which is not demonstrable clinically may become apparent after trauma of the face and may then develop quickly. These changes are possible only when the central regulation has been disturbed, even in a latent or incipient form. An analogous situation may be found in those rare cases of paralysis agitans or amyotrophic lateral sclerosis in which the signs and symptoms start in an extremity that has been subjected to trauma.

Some authors attribute a role in the development of hemiatrophy to infectious disease. Most of these infections are banal and very common in children, and a connection with hemiatrophy is suggested in only a few cases. For instance, in the cases of Popova [203] and Kroll [47] hemiatrophy appeared after typhoid. When the slow hemiatrophic process is already at play, a general infection may precipitate the development of the disease. It is known that intercurrent infection may influence even such diseases as neurofibromatosis by exciting the growth of new fibromas or by causing more pigmented patches (Wilson). That heredodegeneration may develop in association with a general infectious disease is well known and has been stressed, especially by Jendrassik.[14] The congenitally weak trophic mechanism can perform its work while the organism is in good health, but it fails when higher requirements are put on it after an infection.

As heredodegeneration, hemiatrophy may be compared to other diseases based on constitu-

203. Popova, N.: Pathology and Therapy of the Hemiatrophia faciei et corporis, Sovrem. psikhonevrol. **4**:475, 1927.

tional inferiority of certain centers and systems, such as narcolepsy, torsion dystonia, paralysis agitans and amyotrophic lateral sclerosis. Such a condition usually develops on the basis of an autochthonous primary systemic degeneration. This, then, is the genuine, idiopathic form of the disease. But clinically identical syndromes may be attributed to an endogenous factor. Among these factors encephalitis plays a leading role. In narcolepsy a genuine and a symptomatic form are distinguished. Torsion dystonia may develop on the basis of an autochthonous degeneration of the corpus striatum, but in some instances it is definitely postencephalitic. The same is true of paralysis agitans. Amyotrophic lateral sclerosis has been seen after encephalitis. These examples could be multiplied; they show that the same syndrome may be produced by a central lesion of particular location, regardless of its cause. Therefore it is understandable that hemiatrophy, which usually develops on a degenerative basis, may be due to some other local process, such as encephalitis. In some instances the relation to encephalitis is so close that it warrants the assumption of a causative connection between the two diseases. Reference may be made to the cases of Chasanow,[46] Kirschenberg,[183] Kroll,[47] Mankowski,[192] Meyer,[19] Recht [114] and Sterling.[204] Even in these clearcut cases of facial hemiatrophy which occurred after the onset of encephalitis, a latent, slowly progressing degeneration may have been at play. If so, the assumption would be that the patient had been born with feeble trophic centers, which were unable to withstand, in addition, the impact of a disease and that these centers suffered from it more than the other parts of the brain. In rare instances, hemiatrophy, like parkinsonism, has been attributed to arteriosclerosis (Stief [78] and Süss [185]) and to syphilis (Graff,[160] Jolly and Bassi,[205] Lewin,[206] Recht,[114] Salomon [126] and Vivado [24]). In only 1 case was it attributed to multiple sclerosis (Jolly [67]).

The apparent relationship of facial hemiatrophy to progressive lipodystrophy, which was discussed in a previous paper (Wartenberg [2]), also suggests a possible central origin. As previously stated, the atrophy of the fat tissue is the primary and dominant feature of hemiatrophy. Bilateral hemiatrophy, which is not uncommon, closely resembles lipodystrophy. In some cases of facial hemiatrophy—for instance, in my case 4—the disorder could be called unilateral facial lipodystrophy. Both diseases may, in rare instances, be hereditary. Both have complete and incomplete forms. In hemiatrophy the process transgresses the boundary of the face, while in lipodystrophy a concomitant involvement of the skin occurs. In some cases the differential diagnosis has been so difficult as to warrant a detailed discussion. The case of Wolff and Ehrenclou [181] presented features of both hemiatrophy and lipodystrophy. Many authors have stated that lipodystrophy is due to a centrally located lesion, and some assumed an underlying degenerative or encephalitic process.

The following hypothesis as to the origin of hemiatrophy, although highly speculative, may be worth mentioning. In heredodegenerative disease involving the brain there is disintegration of the highest cerebral function. In narcolepsy, for instance, a disintegration of the sleep components occurs, and in paralysis agitans there is loss of erect posture. If one assumes that a brain center or centers regulate the simultaneous and proportionate growth of both halves of the body and cement them into a compact unit, then progressive facial hemiatrophy, from the pathophysiologic standpoint, may be the first step in an attempt to dissolve this trophic unit of the organism into lateral halves. This process would be a kind of schizotrophia sagittalis. Pictures of patients with beginning or abortive hemiatrophy who have a sharply defined sagittal line of atrophy in the paramedian area seem to confirm that an attempt, so to say, is being made here to separate the body into lateral halves. Thus considered, hemiatrophy would be a disturbance of the hypothetic brain centers which integrate the lateral halves of the body and would represent a failure in the fusing function of these centers.

In order to bring some clarity into the kaleidoscopic clinical picture of facial hemiatrophy, attention has been focused on some aspects of the disease, while it has been diverted from others. There was no other way of bringing order into the maze. No hypothesis is, or ever will be, able to explain every sign and symptom in every case of hemiatrophy. Although the ideas on the pathogenesis of hemiatrophy developed in this paper have been most critically scrutinized, no definite conclusions could be established.

SUMMARY

In cases of facial hemiatrophy, the hair of the skull and of the face is affected frequently and at an early stage. This involvement may take the form of a circumscribed alopecia or of blanching of the hair and may precede other symptoms.

204. Sterling: Hémiatrophie faciale, Rev. neurol. **34**: 138, 1927.

205. Jolly and Bassi, cited by Oppenheim.[29]

206. Lewin: Ueber die bei halbseitigen Atrophien und Hypertrophien, namentlich des Gesichtes, vorkommenden Erscheinungen, Charité-Ann. **9**:619, 1884.

The dermatologic manifestations of hemiatrophy usually start in the paramedian area of the face. This area is a vertical streak of about 1 or 2 fingerbreadths running parallel and lateral to the midline.

The existence of a disease called abortive progressive facial hemiatrophy is assumed. Its minimal atrophic changes are located in the paramedian area and become stationary for years.

So-called *sclerodermie en coup de sabre* is apparently nothing but such an abortive progressive facial hemiatrophy.

Not only hemiatrophic and sclerodermatous manifestations, but often congenital malformations of the skin, are located in the paramedian area.

The paramedian area corresponds to the vertical line of the body at which the bilateral trophic influence of the brain centers ceases and the unilateral influence begins.

The brain, especially on the affected side, often shows involvement. Contralateral epilepsy is the most conspicuous symptom of such involvement.

The fundamental manifestation of hemiatrophy is the atrophy of the fat and subcutaneous tissues.

The hemiatrophic changes may extend in various degrees from the area of the face to the homolateral parts of the body.

A patient with hemiatrophy may show, on the homolateral side of the body, abortive or latent symptoms of an atrophic process.

The pathologic process which leads directly to hemiatrophy is regarded as an active one and is due to a state of irritation in the peripheral trophic sympathetic nervous system.

In the areas of hemiatrophy, phenomena of irritation of the sympathetic, the cranial and the spinal nerves are often found. They may be explained by an irritation transmitted from the sympathetic trophic system to other systems.

Inflammatory processes are often found in the areas of hemiatrophy. They have a predilection for localization in the hemiatrophic area because the sympathetic innervation there is disturbed.

The concomitant involvement of the brain homolaterally which leads to epilepsy may be explained by disturbance of the cervical sympathetic system, which innervates the vessels of the brain. This disturbance creates a locus minoris resistentiae for toxic or infective processes.

Thus, hemiatrophy is not due to a primary inflammatory process in the peripheral sympathetic nervous system. The primary process is elsewhere, but it indirectly weakens the resistance of the affected tissues to toxi-infections.

The irritation in the peripheral sympathetic nervous system that causes hemiatrophy is a release phenomenon. It is due to disturbance of the higher centers, which leads to increased and unregulated activity of the lower centers. This phenomenon is analogous to that seen with lesions of the higher centers of the pyramidal and extrapyramidal motor systems.

The etiologic process in hemiatrophy may be encephalitis. Usually it is a heredodegeneration.

As heredodegeneration, hemiatrophy may be compared to torticollis, narcolepsy, paralysis agitans and similar diseases.

The exogenous factors that have been incriminated as causes of hemiatrophy are inadequate to explain the disease. The course of the disease is one typical of a heredodegeneration.

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LOCALIZING VALUE OF TEMPORAL CRESCENT DEFECTS IN THE VISUAL FIELDS

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The fact that the most peripheral portion of the temporal field has an unpaired representation in the optic pathways and visual cortex has been well recognized. The field of the two eyes, together, or the binocular field, is the combination of the right and the left uniocular field. These partly overlap, so that the nasal field of one eye covers the greater portion, the paired portion, of the other, leaving an outer, crescentic, uniocular area unpaired. This unpaired portion is called the temporal crescent or "half-moon" (fig. 1). The paired portion has a diameter of approximately 120 degrees; the unpaired portion extends for 30 to 40 degrees on each side beyond the paired portion.

The fibers of the peripheral portion of the nasal retina pass in the medial portion of the optic nerve.[1] However, the most distal point of the visual pathway at which the fibers of the temporal crescent form a distinct and separate bundle is in the chiasm. Wilbrand's[2] study demonstrated that here they were situated ventrolaterally. These fibers from the nasal retina then pass in the most ventral portion of the tract and to the ventral portion of the lateral geniculate body.[3] According to Kronfeld,[4] there is a gap in knowledge as to the exact pathway of these "half-moon" fibers, from the external geniculate body through the subcortical area to the calcarine fissure.

Traquair[1] plotted the course in the medial portion of the optic radiation, both above and below the posterior horn of the ventricle, to end in the most anterior portion of the area striata.

Bender and Strauss[5] inferred that the fibers for vision in the temporal crescent traverse the ventral part of the optic radiations. Their conclusion was based largely on the work of Pfeiffer[6] and Poliak.[7] Pfeiffer stated the belief that all the fibers reach the cortex by passing below the posterior horn, while Polyak suggested that the calcarine fissure is reached by passing over the posterior horn as well.

Kronfeld[4] stated that the cortical representation of the temporal half-moon can exist in the lower lip of the calcarine fissure alone. However, he also asserted that the crescent may be represented above as well as below the calcarine fissure, the portion above representing the lower half, and that below the upper half, of the temporal crescent in the visual field.

It is conceivable that interference with this pathway at any point may result in a temporal crescent defect in the visual field. The studies of Traquair[8] indicated that a uniform depression of the visual field may first show a loss of the temporal half-moon. This Kronfeld[4] called a "pseudo temporal half moon." Such a finding may occur with a diffuse lesion of the optic nerve. With careful perimetric tests the inner isopters will also be found to be contracted and will thus indicate the general depression.

Lesions of the chiasm may also produce temporal crescent defects. Aneurysms of the carotid artery, tumors, anything pressing below and from the side, may catch the temporal crescent fibers. However, most changes in the fields due to lesions in the chiasmal region are bilateral;

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1. Traquair, H. M.: An Introduction to Clinical Perimetry, ed. 3, St. Louis, C. V. Mosby Company, 1940, p. 74.

2. Wilbrand: Schema des Verlaufs der Sehnervenfasern durch das Chiasma, Ztschr. f. Augenh. **59**:135, 1926.

3. Brouwer, B., and Zeeman, W. P. C.: The Projection of the Retina in the Primary Optic Neuron in Monkeys, Brain **49**:1, 1926.

4. Kronfeld, P. C.: The Temporal Half Moon, Tr. Am. Ophth. Soc. **30**:43, 1932.

5. Bender, H. B., and Strauss, I.: Defects in Visual Field of One Eye Only in Patient with a Lesion of One Optic Radiation, Arch. Ophth. **17**:765, (May) 1937.

6. Pfeiffer, R. A., in Schieck, F., and Brückner, A.: Kurzes Handbuch der Ophthalmologie, Berlin, Julius Springer, 1930, vol. 1, p. 426.

7. Poliak, S.: The Main Afferent Fiber Systems of the Cerebral Cortex in Primates, Berkeley, Calif., University of California Press, 1932, vol. 2, p. 370.

8. Traquair, H. M.: Essential Considerations in Regard to the Field of Vision; Contraction or Depression? Brit. J. Ophth. **8**:49, 1924.

in addition, careful perimetric studies in a case of pituitary tumor may often show hemichromatopsia, even in the early stages, which will aid in localizing the lesion. Although the occurrence of a unilateral cut in the temporal crescent due to a lesion in the region of the chiasm is conceivable, it is not likely, as the fibers in this region are too compact. Also, central vision would most likely be involved by a lesion in this area because of the proximity of the macular fibers. Kronfeld [4] could find no proved cases in the literature of isolated unilateral defects of the temporal half-moon from lesions of the chiasma or the optic tract.

Lesions above the external geniculate body can produce a uniocular temporal crescent defect in the visual field by involving the radiations in the temporoparieto-occipital area or the anterior tip of the visual cortex itself.

Lutz [9] reported several cases in which a defect existed only in the uniocular field of vision. Behr [10] observed several cases in which at cer-

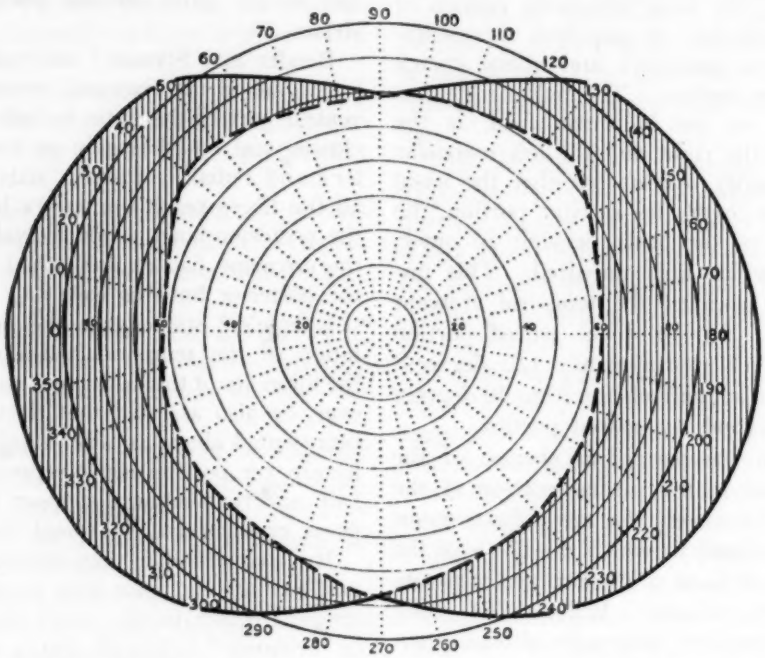

Fig. 1.—The binocular field, showing the crescentic unpaired areas (taken from Traquair [1]).

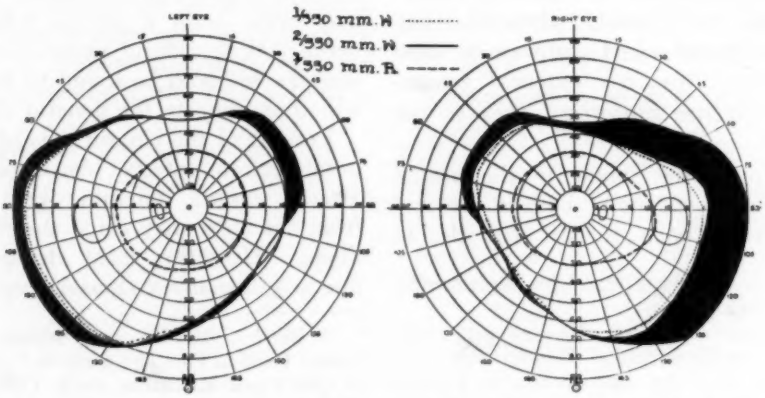

Fig. 2 (case 1).—Perimetric fields taken April 8, 1928, wtih vision of 6/9 in each eye.

9. Lutz, A.: Ueber asymmetrische homonyme Hemianopsie und Hemiakinesis pupillaris, Arch. f. Ophth. **116**:186, 1925.

10. Behr, C.: Die homonymen Hemianopsien mit einseitigem Gesichtsfelddefekt im "rein temporalen halbmondförmigen Bezirk des binokularen Gesichtsfeldes," Klin. Monatsbl. f. Augenh. **56**:161, 1916.

tain stages of disease of the central visual tract a defect in the uniocular temporal crescent was present alone.

Kronfeld [4] presented 26 cases from the literature and 3 of his own, demonstrating various lesions in which the temporal crescents were of defect existed in the periphery of the temporal field of vision. They concluded that an unpaired peripheral scotoma indicates an early defect in the optic radiations and that such a finding has localizing value in the early diagnosis of tumor of the brain.

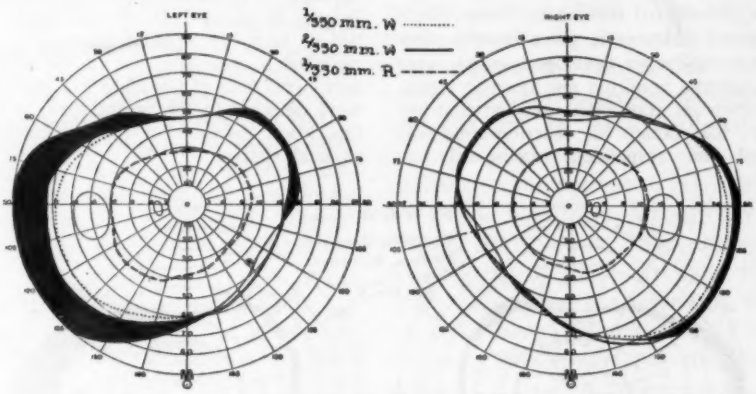

Fig. 3 (case 2).—Perimetric fields, with vision of 6/6 in each eye.

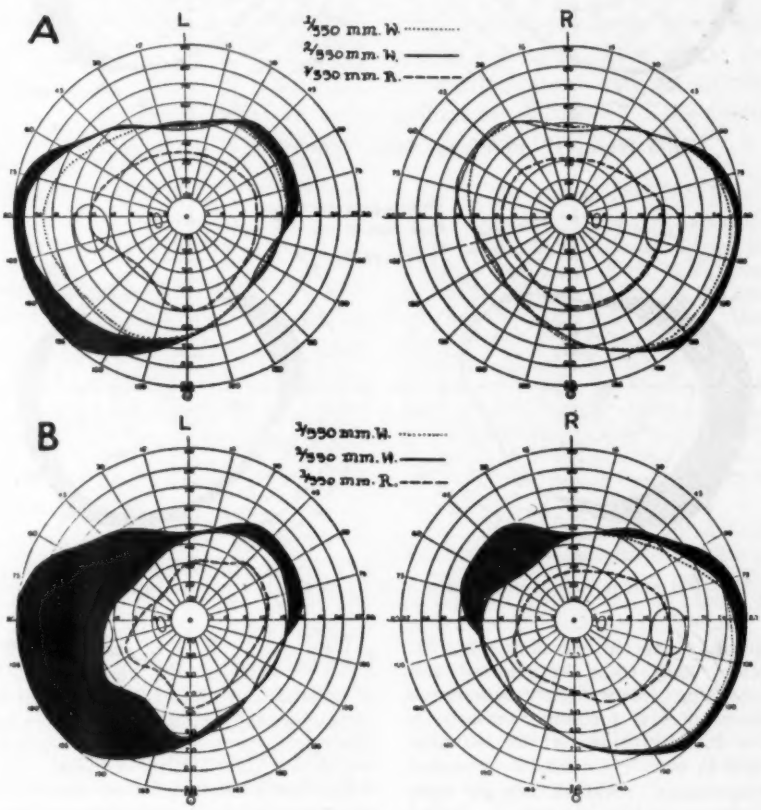

Fig. 4 (case 3).—Perimetric fields taken (*A*) before operation and (*B*) two months later.

importance either by their absence or by their presence.

Bender and Strauss [5] reported 10 cases in which, as a result of lesions of the optic radiations, an unpaired crescentic or hemicrescentic

It is the purpose of this paper to substantiate these observations of Bender and Strauss with 5 verified cases of brain tumor and to emphasize the value of this sign as an aid in the practical localization of a pathologic cerebral process.

REPORT OF CASES

CASE 1.—G. J. Mc., a 43 year old minister, complained of numerous "nervous breakdowns" over a period of five years. An automobile accident, two years prior to operation, in which the patient suffered a minor cranial trauma, occasioned a roentgenographic examination of his skull, which showed "thickening of bone of the left parietal region." Eight months before admission he had a generalized convulsion, from which he completely recovered. However, seven months after this convulsion severe headaches developed, which were soon followed by projectile vomiting and blurred vision. Neurologic examination on admission revealed that the patient was drowsy; but though his reaction time was considerably slowed, he responded intelligently to questions. The respiratory rate on occasions fell to 12 per minute. A decided lump could be palpated over the left parietal region. Neurologic examination revealed nothing significant save for some weakness of the left hand and a Babinski sign on the left side. Visual acuity was 6/9 in each eye without correction. Ophthalmoscopic examination revealed normal optic nerve heads. Perimetric studies showed a distinct crescentic cut in the right field of vision, without any changes in the central field (fig. 2). Roentgenographic studies gave evidence of atrophy of the dorsum sellae and an area of hyperostosis of the left parietal region. Operation at the site of the hyperostosis revealed a large meningioma in the left parieto-occipital region.

CASE 2.—M. B., a 35 year old woman, complained of headache of one year's duration and vertigo with change of position for six months. She had had progressive left hemiparesis and recurrent sensory jacksonian seizures on the left side for six months. Neurologic examination revealed spastic left hemiparesis and impaired sense of position of the left large toe and thumb. There were a Babinski sign and ankle clonus on the same side. Roentgenograms of the skull showed atrophy of the dorsum sellae. The spinal fluid pressure was normal. Ophthalmoscopic examination disclosed papilledema of about 1 D. in each eye. Visual acuity was 6/6 in each eye without correction. Perimetric studies revealed a crescentic cut in the left visual field. The peripheral field of the right eye was full, and no changes were detected in the central field of either eye (fig. 3). Operation disclosed a large meningioma of the right parietal region.

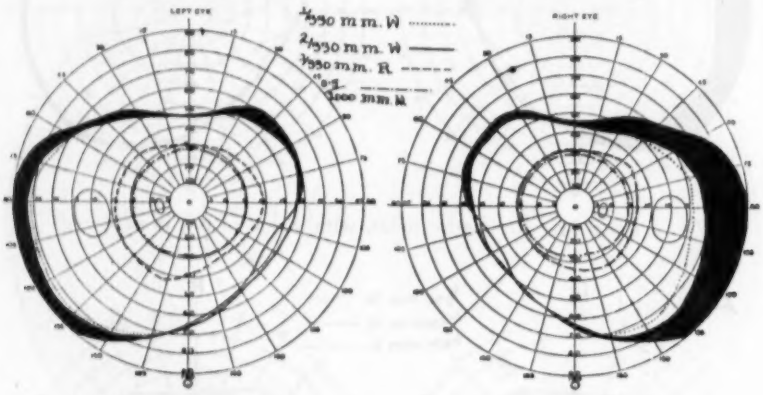

Fig. 5 (case 4).—Perimetric fields, with vision of 6/6 in each eye.

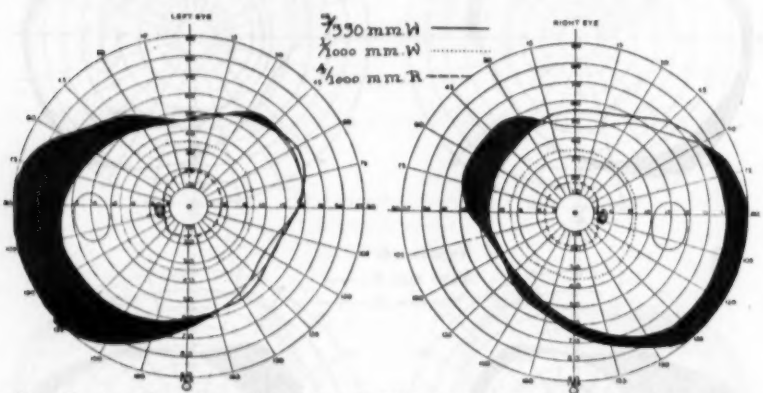

Fig. 6 (case 5).—Perimetric fields, with vision of 6/12 in the left eye and of 6/9 in the right eye.

CASE 3.—M. F., a 22 year old woman, had had headaches for eight months, together with seizures consisting of opisthotonos and exacerbations of headache. The results of neurologic examination were essentially negative. Roentgenograms of the skull revealed calcification deep within the right parieto-occipital area. The optic disks were slightly blurred, but no measurable elevation of the margins existed. Visual acuity was 6/6 in each eye without correction. Determination of the visual fields revealed only a temporal crescent cut in the left visual field, without changes in the central field in either eye (fig. 4 *A*). The operation was done in two stages. In the first procedure, a bone flap was turned down in the parieto-occipital region but the dura was not opened. Perimetric examination performed four weeks after the first surgical procedure showed an incongruous left homonymous hemianopsia (fig. 4 *B*). Subsequently the tumor

was exposed and proved to be a well demarcated cystic astrocytoma deep in the right parieto-occipital region.

CASE 4.—J. L. W., a 57 year old man, had shown personality changes for six months and progressive aphasia for four months. He had had weakness of his right hand for four weeks and weakness of his right leg for two weeks. Neurologic examination showed right hemiparesis, most marked in the upper extremity, together with hyperreflexia, a Babinski sign and ankle clonus, all on the right side. There were distinct hypesthesia and hypalgesia on the same side. Astereognosis was present in the right hand. The position sense in the right large toe and the right hand was notably impaired. His aphasia appeared to be predominantly of the sensory type. Roentgenograms of the skull and the ocular fundi were normal. Visual acuity was 6/6 in each eye with correction. Determination of the visual fields disclosed a temporal crescent defect in the right visual field (fig. 5). Operation revealed a large cystic glioma of the left parietal area.

CASE 5.—I. M., a 51 year old man, had been drowsy for one month. Headache was said to be of only one week's duration, but he had had a progressive left hemiparesis for one month. He was admitted to the hospital, after having been comatose for twenty-four hours. Examination on admission disclosed spasticity of all four extremities, a stiff neck and a positive Babinski sign on the left side. Ophthalmologic examination had been done three weeks prior to admission and revealed a visual acuity of 6/9 in the right eye and 6/12 in the left eye without correction. The fundi were normal. Determination of the visual fields at this time revealed the temporal crescent defect in the left visual field and no sign of changes in the central field (fig. 6). Operation exposed a glioblastoma multiforme of the right temporoparietal area.

COMMENT

These cases are presented to emphasize that careful perimetric studies may reveal a defect in one unpaired portion of the visual field, i. e., the temporal crescent, which is of practical importance to the neurologist and the neurosurgeon. A uniocular crescent defect would indicate the laterality and general area involved by a tumor or other pathologic process.

No exact anatomic information may be derived from these cases. The position of the tumor itself may not tell the entire story, for cerebral tumors produce edema and other distant reactive phenomena which may also cause disturbances in the fields of vision. However, in all these 5 cases the suprageniculate pathways and, more definitely, the ventromedial portion of the radiations in the parietal, temporoparietal and parieto-occipital areas were involved.

A unilateral temporal crescent defect alone is not a common finding. The incidence reported by Bender and Strauss in 100 cases of verified tumors in which the fields could be plotted was 10 per cent. Several hundred of the neurosurgical records of Dr. Charles H. Frazier and Dr. Francis C. Grant had to be searched before finding these 5 cases. The vast majority of the tumors involving the optic radiation show further advanced changes in the visual fields, such as homonymous hemianopsia. A uniocular crescent cut is usually disregarded. Case 3 beautifully demonstrates the advance from a unilateral crescent cut to bilateral involvement of the field, toward a homonymous hemianopsia. Bender and Strauss have previously noted that, irrespective of the location of the lesion in the optic radiation, homonymous anopsias usually begin in the periphery and advance toward the center. This brings out the importance of the temporal crescent defect as an early localizing sign.

SUMMARY

In 5 cases presented here, uniocular temporal crescent defects in the visual field were due to verified cerebral tumors involving the suprageniculate pathway. This finding is important as an early localizing sign.

DISCUSSION

DR. JOSEPH C. YASKIN, Philadelphia: The chief value of this contribution is that the presence of the temporal crescent defect in the absence of a nasal defect on the opposite side should arouse suspicion of the involvement of the contralateral visual pathways behind the primary visual centers. I am surprised that so few examples of this sign were found in the large collection of cases of tumor. I should like the authors to state how frequently this defect is observed in cases of chiasmal syndromes to which they alluded.

The authors' observations on small defects of the temporal field are valuable when these defects are found to be constant by repeated studies.

DR. HENRY SHENKIN, Philadelphia: Dr. Yaskin asked about chiasmal lesions. I have no doubt that they occur frequently; however, since the chiasmal fibers are so compact, defects due to lesions of the chiasma will tend to be bilateral, not unilateral.

Kronfeld was unable to find in the literature a case of a unilateral crescent defect due to a chiasmal lesion. Kronfeld's paper appeared in 1932, and no such case has since been reported.

These defects are often overlooked. I think that a 5 degree difference between the two fields should be regarded as significant.

Hospital of the University of Pennsylvania.

DEGENERATION OF PERIPHERAL NERVES IN PERNICIOUS ANEMIA

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The signs and symptoms of disease of the peripheral nerves associated with pernicious anemia and subacute combined degeneration have been noted by a number of observers, estimates of the incidence varying from 4.9[1] to 23[2] per cent. The separation of neuritic from myelitic components in a diffuse disease of the nervous system is notoriously difficult and unreliable, and for this reason the status of the peripheral nerves in this disorder has been speculative and controversial. Since peripheral nerves have a powerful regenerative capacity as compared with the insignificant recuperative powers of the central nervous system, the presence and degree of neuritic damage in pernicious anemia are important in prognosis and therapy. This report describes the pathologic changes in the peripheral nerves in 4 cases in which autopsy was performed and the results of biopsy of a peripheral nerve in an additional case.

REPORT OF CASES

CASE 1.—N. B., a 66 year old white woman, was found elsewhere to have pernicious anemia in 1928 and was treated with oral and parenteral administrations of liver extract until 1941, when she discontinued all treatment. Anorexia, alternating diarrhea and constipation, weakness and intellectual impairment appeared and progressed insidiously in the twenty-five month period between cessation of therapy and her admission to University Hospital.

The patient was pale, cachectic, dehydrated and in a severe confusional state. The knee and achilles jerks were absent, and there was a bilateral extensor plantar response. Vibratory sensation and the sense of position were absent in the lower extremities, and she was incontinent of urine and stool. The hemoglobin of the blood measured 3.2 Gm. per hundred cubic centimeters; the red cell count was 600,000 and the white cell count 2,250 per cubic millimeter, and the mean corpuscular volume of the red blood cells was 133 cubic microns.

Transfusions and parenteral administration of liver extract were begun, but pneumonia resulted in death seven days after her admission to the hospital, and fifteen years after onset of the disease.

Pathologic examination showed acute purulent bronchitis, lobular pneumonia and advanced chronic atrophic gastritis. Bone marrow from a rib, the sternum and a vertebral body had a cellular content averaging 90 per cent and contained numerous immature cells and megakaryocytes.

The brain was not examined. The spinal cord showed demyelination, vacuolation and gliosis in the gracile component of the posterior column and gliosis in the intramedullary course of the entering posterior root fibers (fig. 1); the cuneate component of the posterior column and the lateral columns presented similar changes of minimal degree. There was a diffuse increase in Marchi globules, most marked in the posterior columns and in the intramedullary course of the posterior root fibers. Nissl's chronic cell disease was present in numerous anterior horn cells, which showed corkscrew dendrites, pyknosis and poor or no differentiation between nucleus and cytoplasm.

About 25 per cent of the ganglion cells of the posterior root ganglia (lumbosacral segments) were normal (fig. 2). The remainder showed varying degrees of degenerative change, ranging from fraying of the cell margins, vacuolar cell change and reduction of Nissl substance to fine, dustlike particles, to complete dissolution of the cell and its replacement by proliferated capsular cells and connective tissue. Mild Marchi degeneration was present in segments of the brachial plexus, and the femoral nerve showed a pronounced distortion of myelin sheaths and increase in Marchi globules. Sections of the posterior roots and the femoral nerve stained with azocarmine showed hypertrophy and hyperplasia of the Schwann cells, reduction in myelin sheaths and axis-cylinders and a substantial increase in the endoneurial connective tissue.

CASE 2.—A. G., a 67 year old lumberman, was admitted to University Hospital because of complete paralysis of the lower extremities, of six months' duration. His neurologic symptoms were of fifteen years' standing and had begun with numbness and tingling in the hands and feet. Weakness and ataxia had been intermittent during this period; an exacerbation of this weakness and unsteadiness in the legs had begun twelve months prior to his admission, and he had been bedfast for six months prior to examination at this hospital.

He presented a simple organic dementia. The upper extremities were paretic, atrophic and ataxic, and the biceps and triceps reflexes were diminished. There was complete paraplegia in flexion with bilateral foot drop in the lower extremities, accompanied with secondary joint contractures at the hips and knees; muscular tone was increased, and there was moderate atrophy. The knee and achilles jerks were absent, and there was a bilateral Rossolimo sign but no extensor plantar response. Sense of position and vibratory sensation were absent in the lower extremities, and superficial

From the Department of Neurology and the Neuropathology Laboratory of the Neuropsychiatric Institute, the University Hospital and the University of Michigan Medical School.

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2. Dynes, J. B., and Norcross, J. W.: Peripheral Neuritis as a Complication of Pernicious Anemia, J. A. M. A. **122**:586-588 (June 26) 1943.

sensation was diminished below the knees. He was incontinent of urine and stool. Physical and roentgenographic signs of pulmonary tuberculosis were likewise present. The hemoglobin of the blood measured 7.7 Gm.; the red cell count was 2,000,000 and the white cell count 3,050 per cubic millimeter, and the mean corpuscular volume of the red blood cells was 120 cubic microns. There was complete gastric achlorhydria.

Parenteral injections of liver extract produced improvement in the blood values, but death resulted from pulmonary tuberculosis one and a half months after his admission.

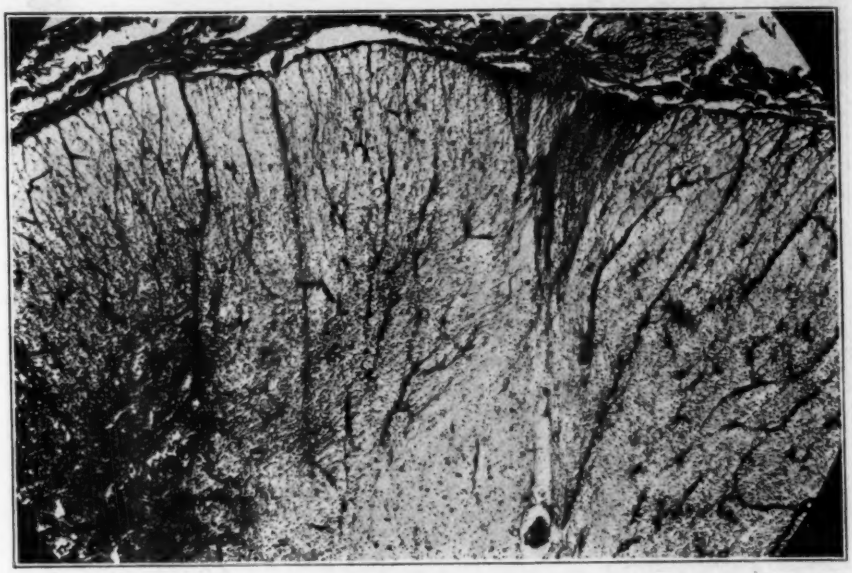

Fig. 1 (case 1).—Severe gliosis in the gracile component of the posterior column of the middorsal portion of the cord (at left) and increase in glia fibers in the course of the intramedullary fibers of the posterior root (upper right portion). Holzer stain for glia fibers; Zeiss planar lens 20 mm.

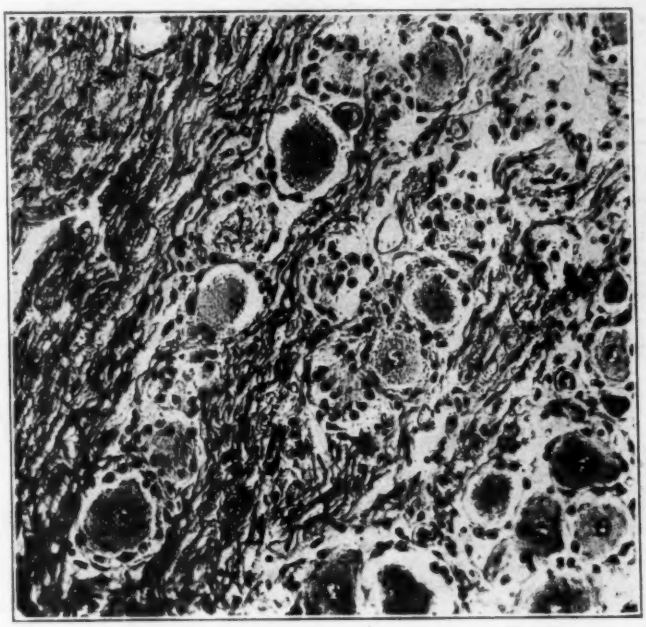

Fig. 2 (case 1).—Regressive changes in the posterior root ganglion of a lumbar segment: pyknosis, neuronophagia and replacement of ganglion cells by proliferations of capsular cells. Azocarmine stain; Zeiss planar lens 20 mm., ocular 2.

Pathologic examination showed tuberculous cavitation in the left lung; epithelioid tubercles in the spleen, liver and bronchial lymph nodes; atrophic gastritis, and chronic cholecystitis with cholelithiasis. Bone marrow

from a rib, the sternum and a vertebral body had a cellular content averaging 50 per cent and contained numerous megakaryocytes.

matter (fig. 3), for the most part perivascular, although this relationship was not always apparent; the Holzer stain for glia fibers demonstrated fine, radiating glia

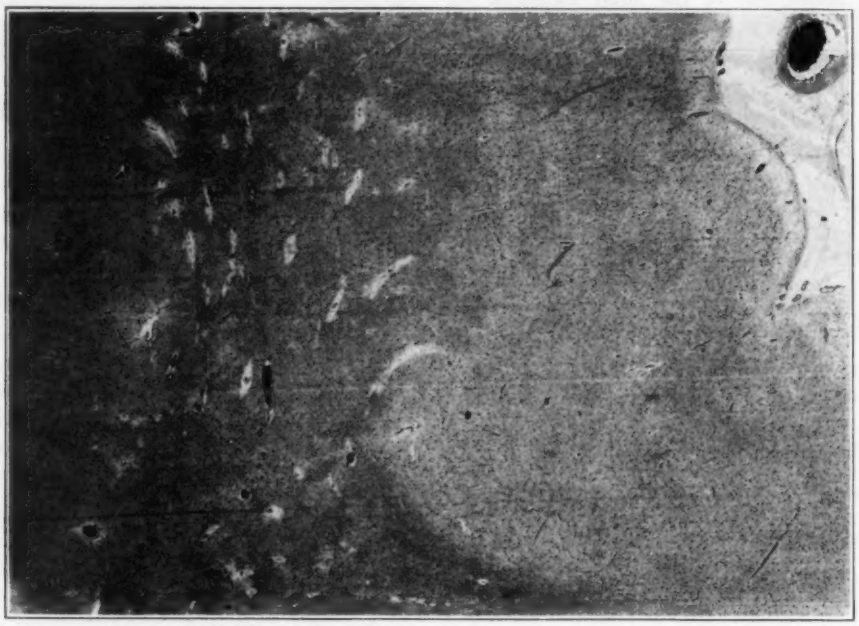

Fig. 3 (case 2).—Areas of perivascular demyelination in the subcortical white matter of the frontal lobe. Hematoxylin and eosin stain; Zeiss planar lens 20 mm.

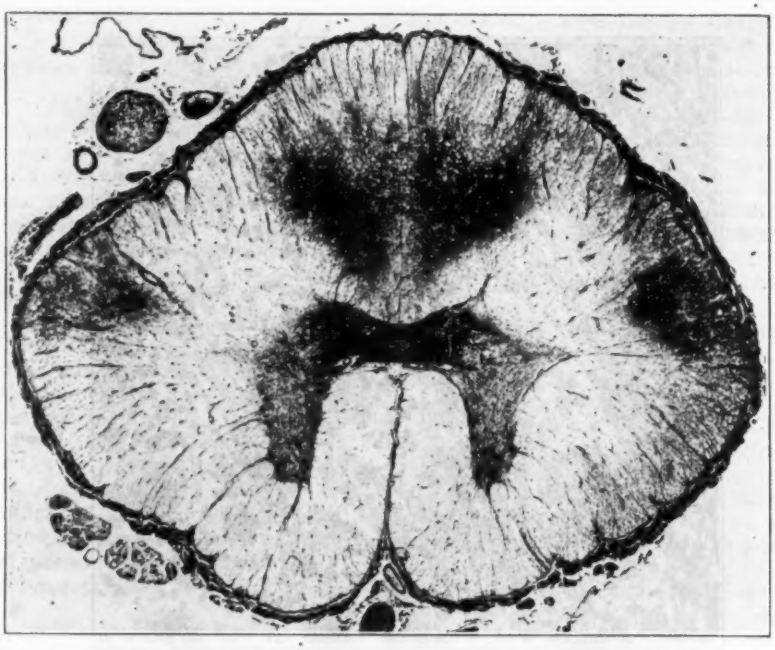

Fig. 4 (case 2).—Increase in glia fibers in the posterior and lateral columns of the middorsal portion of the cord, with vacuolation in the same areas; gliosis in the gray matter, particularly around the central canal, and increase in glia fibers in the intramedullary fibers of the right posterior root. Neurologic symptoms had existed for fifteen years; no liver treatment had been given until one and a half months before death. Compare with figure 7. Holzer stain for glia fibers; Zeiss planar lens 50 mm.

There were no signs of tuberculosis in the nervous system. Numerous areas of rarefaction and demyelination were distributed throughout the subcortical white

fibers from the blood vessels in the areas of demyelination. No abnormalities were found in the basal ganglia or the brain stem. There were advanced gliosis

and vacuolization in the posterior columns of the spinal cord, with less severe changes in the lateral columns (fig. 4). Glia fibers were diffusely increased throughout the gray matter, being of greatest density around the central canal. Numerous Marchi globules followed the course of entering posterior root fibers. The ventral horn cells were well preserved.

Azocarmine preparations of the femoral and sciatic nerves showed loss of myelin and axis-cylinders and proliferation of Schwann cells, of lesser severity than in case 1.

CASE 3.—A. H., a 56 year old white woman, had had remissions and exacerbations of weakness, ataxia and

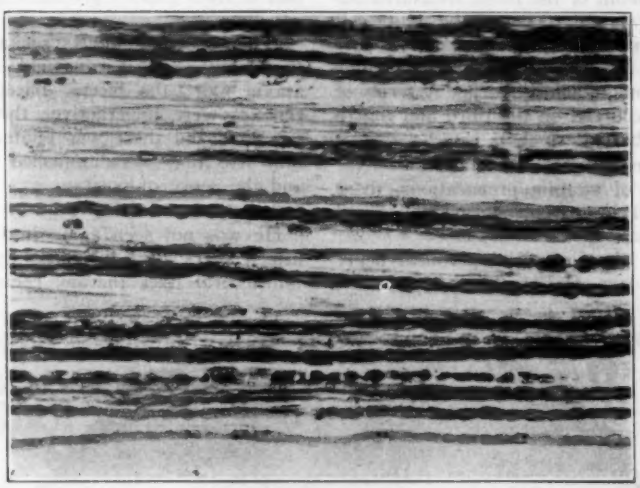

Fig. 5 (case 2).—Beaded, tortuous myelin sheaths and formation of Marchi globules in the superficial peroneal nerve. Marchi stain; Zeiss planar lens 20 mm., ocular 2.

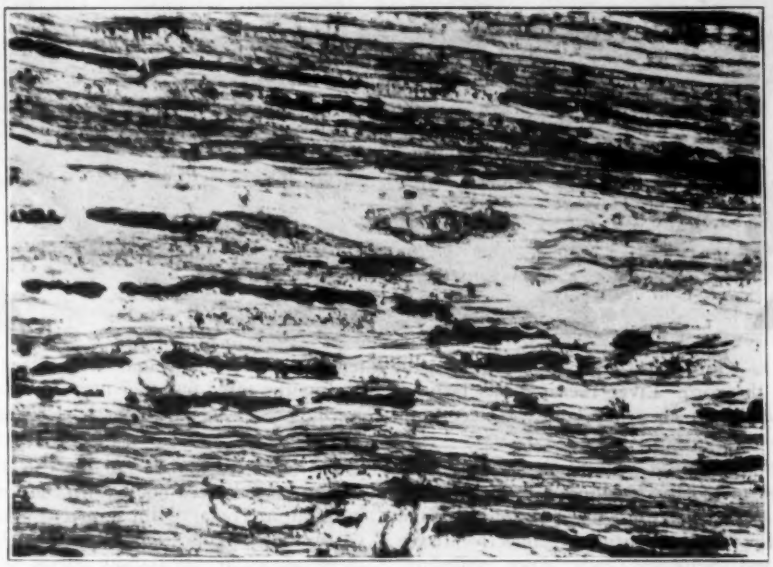

Fig. 6 (case 3).—Numerous intracellular, extracellular and perivascular Marchi globules in the superficial peroneal nerve. Marchi stain counterstained with azocarmine; Zeiss planar lens 20 mm., ocular 2.

Approximately 35 per cent of the ganglion cells of the posterior root ganglia in the lumbosacral segments were normal, the others showing degenerative cellular changes and proliferation of the capsular cells, as in case 1. Minimal Marchi degeneration was present in the nerve fibers of the brachial plexus, moderately severe changes in the femoral nerve and advanced Marchi degeneration in the superficial peroneal nerve (fig. 5).

inability to walk for twenty-four years. She had been confined to bed for the preceding eight months with headache, anorexia, increasing paralysis of the lower extremities, intermittent incontinence of urine and stool and progressive edema.

On admission to University Hospital, she was acutely ill and cachectic, with peripheral edema to the sacrum, ascites and a distended bladder. There were mild intel-

lectual loss; bilateral nerve deafness; spasticity, paresis, ataxia and atrophy in the upper and lower extremities, and hyperactive deep tendon reflexes bilaterally, with the Hoffmann sign, an extensor plantar response and ankle clonus on both sides. The sense of position and vibratory sensation were absent in the lower extremities and diminished in the upper extremities, and there were severe distal hypasthesia and hypalgesia in the lower extremities. The hemoglobin of the blood measured 3.5 Gm.; the red cell count was 900,000 and the white cell count 1,350 per cubic millimeter, and the mean corpuscular volume of the red blood cells was 111 cubic microns. There was complete achlorhydria. A series of grand mal convulsions occurred on the third and fourth hospital days but none thereafter.

With transfusions, parenteral administration of liver extract and large doses of vitamin preparations, there was considerable general improvement, and the blood values returned to normal.

A biopsy specimen of the superficial peroneal nerve (fig. 6) was taken forty days after treatment was begun. Marchi sections counterstained with the azocarmine technic showed marked tortuosity, swelling and distortion of the myelin sheaths and numerous Marchi globules from degenerating myelin. The endoneurial connective tissue was increased, and Schwann cells were abundant. The few remaining axis-cylinders showed extensive disintegration.

Case 4.—C. O., a 58 year old real estate dealer, had the onset of numbness and tingling in the hands and feet fifteen months before the initial examination at University Hospital. This was followed by generalized weakness and ease of fatigue, sensations of walking on cotton, vesical incontinence and a weak, staggering gait, which progressed to complete inability to stand without support.

There were gross paresis and ataxia in the lower extremities. The knee and achilles jerks were absent, and there was a bilateral extensor plantar response. Vibratory sensation and the sense of position were diminished in the lower extremities; the bladder was distended. There was no free acid in the gastric contents; the hemoglobin of the blood measured 7 Gm.; the red cell count was 2,040,000 and the white cell count 6,800 per cubic millimeter, and the Price-Jones curve was shifted to the right. Parenteral administration of liver extract produced a satisfactory reticulocyte response.

When the patient was reexamined three years later, the blood values were normal. He walked with a mildly ataxic gait; the biceps, triceps, patellar and achilles reflexes were hyperactive; the plantar responses were extensor, and there was bilateral ankle clonus. Vibratory sensation was diminished in the lower extremities, and the sense of position was intact. The incontinence had disappeared.

He was not seen again in University Hospital until fifteen years after his initial symptoms. He had maintained oral liver therapy regularly and had been able to do light work, but the blood values for this intervening period were not known. He was admitted to the hospital in coma, with severe congestive heart failure of two weeks' duration, manifested by cardiac enlargement, auricular fibrillation, edema of the lungs, ascites and peripheral edema to the sacrum. The hemoglobin of the blood was 16.2 Gm.; the red cell count 5,100,000 per cubic millimeter, and the mean corpuscular volume of the red blood cells was 103 cubic microns. He failed to improve with administration of oxygen, digitalis and mercurophylline and died three days after admission.

Pathologic examination showed old and recent myocardial infarctions; ventricular thrombi with infarctions in the lungs, kidneys and liver; congestion of all viscera, and anasarca. Bone marrow from a vertebral body, a rib and the sternum showed congestion and a cellular content averaging 80 per cent.

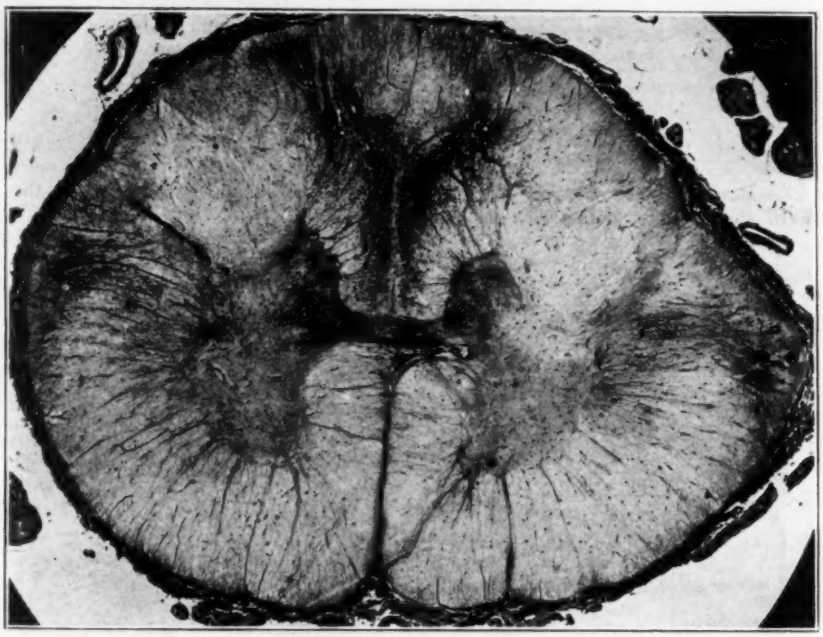

Fig. 7 (case 5).—Gliosis in the posterior column, the lateral column and around the central canal in the high dorsal portion of the cord. Liver therapy was begun fifteen months after onset of neurologic symptoms and was continued until death, fifteen years later. Holzer stain for glia fibers; Zeiss planar lens 50 mm.

The spinal cord (fig. 7) showed mild vacuolation and gliosis in the gracile component of the posterior column; there was minimal gliosis in the lateral columns. A mild increase in glia fibers was present in the entering fibers of the posterior roots. Marchi globules were infrequent in the spinal cord; none were found in the intramedullary course of the posterior roots. The ventral horn cells were well preserved, and the gray matter was normal except for a mild increase in glia fibers about the central canal. About 40 per cent of the ganglion cells of the posterior root ganglia of the lumbosacral portion of the cord were normal, the remainder showing fraying of the cell margins, swelling of the nuclei, diminution or absence of tigroid substance, vacuolar degeneration or complete degeneration, with invasion of the ganglion cell space by capsular cells. There was increased connective tissue within the ganglia and in the posterior roots. Marchi degeneration of mild degree was present in the sciatic and femoral nerves; the reticulocyte response followed the parenteral administration of liver extract.

The blood values were maintained within normal limits during the ensuing eleven years with a preparation of powdered stomach and parenteral administration of liver extract. The patient no longer worked as a printer after treatment was begun. He was admitted to the hospital in 1943 because of severe gastrointestinal symptoms, which proved on examination to be due to carcinoma of the stomach, with metastases to the liver. At this time the biceps, triceps and patellar reflexes were diminished; the achilles reflexes were absent, and there was a doubtful extensor plantar response on the right side. Vibratory sensation was diminished but present at the ankles; the sense of position was intact in the toes. The hemoglobin of the blood measured 10.3 Gm.; the red cells numbered 4,000,000 per cubic millimeter, and the mean corpuscular volume of the red blood cells was 80 cubic microns.

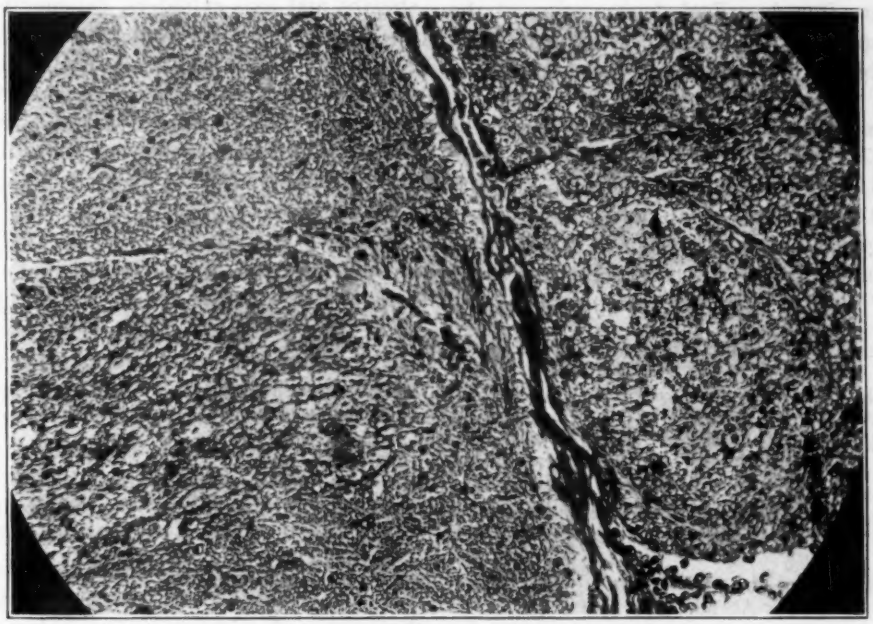

Fig 8 (case 5).—Lumbar segment of the spinal cord (left) and adjacent dorsal root (right) separated by meninges. Demyelination and vacuolation in the intramedullary and extramedullary fibers of the posterior root. Azocarmine stain; Bausch and Lomb 10 mm. lens, ocular 2.

brachial plexus was normal. Both Schwann cells and endoneurial connective tissue were increased in the posterior roots and in the proximal portions of the sciatic, femoral and obturator nerves.

Case 5.—A. K., a 55 year old white man, a printer, was examined in University Hospital in 1932 because of lancinating pains in the feet, of two years' duration. At that time no abnormalities were found at the neurologic or the hematologic examination. The pains continued; and when he was reexamined in 1934, he presented ataxia, spasticity and paresis in the lower extremities, diminished knee jerks, absence of the achilles and plantar reflexes and absence of vibratory sensation and the sense of position in the lower extremities. No free acid was present in the gastric juice after administration of histamine; the hemoglobin of the blood was 11.2 Gm.; the red cell count was 3,410,000 and the white cell count 1,500 per cubic millimeter, and the Price-Jones curve was shifted to the right. A typical

Death was caused by the gastric neoplasm and its metastases six months after admission, thirteen years after the onset of symptoms and nine years after the institution of continuous antianemia therapy.

Pathologic examination showed a small adenocarcinoma of the greater curvature of the stomach, with extensive metastases to the liver and regional lymph nodes, obstructive icterus, cloudy swelling of the liver, edema and ascites. The bone marrow from a rib and a vertebral body was almost exhausted, the cellular content averaging 20 per cent.

Mild posterolateral sclerosis was present in the spinal cord. Marchi preparations of the femoral and sciatic nerves and of the posterior roots showed relatively mild formation of Marchi globules and mild swelling and distortion of the myelin sheaths. Azocarmine sections from the same areas showed increased connective tissue and Schwann cells, particularly in the posterior roots. No abnormalities were found in the brachial plexus.

COMMENT

Pathologic reports describing the status of the peripheral nerves in pernicious anemia are scarce and contradictory; descriptions of cases showing the influence of liver therapy have not been found in the literature. Intact peripheral nerves are described in the pathologic reports of Lichtheim,[3] Minnich,[4] Nonne,[5] Burr,[6] Boedeker and Juliusberger[7] and Homen.[8] Bramwell[9] alleged that the absence of lesions of the peripheral nerves was a characteristic feature of pernicious anemia. Von Noorden,[10] who described severe degeneration of both tibial nerves in 1 case, was apparently the first to verify by pathologic methods the presence of degeneration in the peripheral nerves, and Eisenlohr[11] shortly thereafter described degeneration of the internal saphenous nerve associated with subacute combined degeneration.. Russell, Batten and Collier[12] found severe damage to the peripheral nerves in 1 case, mild degeneration of nerves in 2 cases and no abnormalities of the nerves in 3 other cases. Hamilton and Nixon[13] examined the anterior tibial nerve in 7 cases; Marchi degeneration was present in 6 and Weigert degeneration in 4 cases. Buzzard and Greenfield[14] stated that the peripheral nerves were normal in cases of pernicious anemia, but in a later report, by Greenfield and Carmichael[15] this opinion was reversed; biopsy sections from the anterior tibial nerves of 4 patients with pernicious anemia were stained with osmic acid and compared quantitatively with normal nerves and with nerves degenerated from other causes. The myelin sheaths, particularly among the nerve fibers of larger caliber, were reduced in number in the patients with pernicious anemia.

Cases 1, 2 and 3 in the present series are examples of untreated pernicious anemia of many years' duration, in severe hematologic relapse at the time of pathologic examination. In all there was evidence of degeneration of the peripheral nerves, manifested by reduction in myelin sheaths and axis-cylinders, degeneration of myelin, increase in Schwann cells and endoneurial connective tissue, axonal reaction changes in the ganglion cells of the posterior root ganglia and degenerative changes in the intramedullary course of afferent posterior root fibers. Generalized involvement of the central and peripheral nervous system is illustrated by case 2.

Cases 4 and 5 exemplify treated pernicious anemia, with the patients in hematologic remission at the time of death. The blood values for a thirteen year period were not known in case 4. The patient's bone marrow was moderately hyperplastic; but with the regular intake of liver, the stationary status of symptoms and the normal blood values at the time of his terminal illness, a severe hematologic relapse is unlikely. Moderately severe nerve degeneration was present in this case. In case 5, in which the blood values were known to have been normal for eleven years prior to the terminal illness, there were the fewest signs of degeneration of the peripheral nerve.

It has been frequently observed that the improvement in neurologic function with liver therapy is greatest when there is a scarcity or absence of pyramidal tract signs, i. e., when manifestations commonly assigned to dysfunction of the posterior column predominate. Since such disturbances as ataxia, impairment in vibratory sensation, impairment in the sense of motion and position, diminished intensity or absence of deep tendon reflexes and impaired bladder function may be caused by degeneration of extramedullary nerve pathways, which possess a powerful regenerative apparatus, it is suggested that the improvement with therapy is due to regeneration of peripheral nerves. An optimistic and

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aggressive therapeutic attack is therefore justifiable, contrary to the opinion of some authors,[16] particularly when there is a disorder in those functions shared by the peripheral nerves and the posterior columns of the spinal cord.

SUMMARY

Degeneration of the peripheral nerves was found on pathologic examination in 4 cases of pernicious anemia with posterolateral sclerosis in which autopsy was performed, and biopsy gave evidence of peripheral neuropathy in an additional case. The changes were less severe in the 2 cases in which liver therapy had been given and the patients were not in hematologic relapse at the time of pathologic examination. The great regenerative capacity of peripheral nerves offers an anatomic explanation for the clinically observed improvement with liver therapy in some of the neurologic manifestations of the disorder.

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EMOTIONS AND ADRENERGIC AND CHOLINERGIC CHANGES IN THE BLOOD

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In pursuit of previously published studies,[1] the problem presented itself whether a relationship can be established between substances in the blood having adrenergic and cholinergic properties and specific emotional reactions. Investigations were carried out on patients suffering from various psychopathologic reactions in which different emotions of varying intensity were demonstrable, and on members of the staff and medical students. All subjects were without demonstrable somatic disease.

PHARMACOLOGIC METHODS

The effect of samples of fresh whole blood on the contractions of an isolated strip of the rabbit duodenum was investigated by the following procedure: Healthy adult rabbits were killed by a blow on the head. The intestine was cut at the pylorus, and a strip approximately 10 cm. long was removed immediately and, with careful handling, was washed in Ringer-Tyrode solution. A section from 1 to 1.5 cm. long, attached to a recording lever, was suspended in about 180 cc. of the Ringer-Tyrode solution, and the contractions were recorded on a kymograph. The portion of the duodenum nearest the pylorus was found to be most suitable for the purpose. The solution was gently agitated throughout the experiment by means of a stream of air bubbles. The bottle containing the muscle strip and the Ringer-Tyrode solution was suspended in a water bath at 37 C. (fig. 1).

The blood was drawn from the patient's median cubital vein and mixed immediately with heparin in a small Erlenmeyer flask, and within a period of three minutes 5 cc. was added to the Ringer-Tyrode solution.

All observations were made on two strips of muscle simultaneously. At the conclusion of every experiment the muscle was tested by adding acetylcholine or epinephrine to the solution. The amounts of heparin used were found to be without influence on the spontaneous activity of the muscle or on the response to the pharmacologic agents used.

PSYCHOLOGIC AND PSYCHOPATHOLOGIC CONSIDERATIONS

The emotional reactions studied included anxiety, fear, tension, resentment, anger, depression, elation and sexual excitement. In some experiments, the emotional reactions were clear-cut. In others, two or more emotions were present, frequently making differential evaluations impossible. The emotions were studied by careful observation of the person's behavior before and during the experiment, by ascertaining his subjective detailed description of emotions and sensations in conscious and in dream life and by investigation of the influence of these emotions on attention, concentration, thinking and retention. In psychologic and psychopathologic studies of emotions it has been found that, depending on the type and intensity of the emotions, the aforementioned psychologic functions were affected differently. With these methods of subjective and objective observation and investigation, an attempt was made to evaluate the type, intensity and duration of the emotions before and during the taking of the blood. Anxiety was distinguished from fear by the absence of a definite thought content, a psychologic distinction which has been supported physiologically by their different influence on the dextrose tolerance curve.[2] Tension, which other authors have considered prolonged anxiety, seems to be a special type of

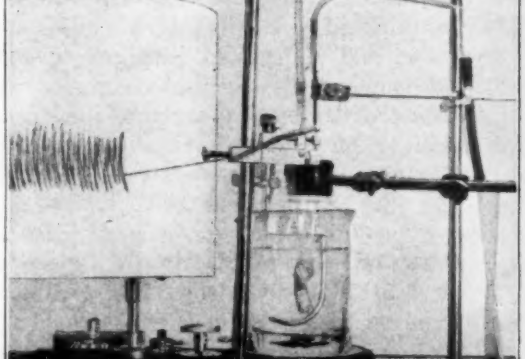

Fig. 1.—Setup of the experiment.

From the New York Hospital and the Departments of Psychiatry and Medicine, Cornell University Medical College.

1. Milhorat, A. T.; Small, S. M.; Doty, E. J., and Bartels, W. E.: Probable Mechanism by Which Somatic Changes in Certain Emotional States Are Mediated, Proc. Soc. Exper. Biol. & Med. **53**:23 (May) 1943.

2. Diethelm, O.: Influence of Emotions on Dextrose Tolerance, Arch. Neurol. & Psychiat. **36**:342 (Aug.) 1936.

emotion, arising from the struggle of contradictory strivings and of seeking difficult goals. The subject feels "taut" and notices sensations of muscular tension, especially in the muscles of the head and neck and, less frequently, of the arms, legs or trunk. Attention, concentration and retention are affected to a greater degree with tension than with anxiety. Anger occurs readily in irritable, tense states. Sometimes anger may be the climax of resentment. This emotion is recognized subjectively in feelings, and, if more intense, objectively in the expression of hostility. Depression and elation are rarely found in psychopathologic states without the accompaniment of anxiety or tension. In this study, depression and elation were observed in pure form in a slight degree, but not in psychopathologic conditions. "Sexual excitement" is a frequently used but ill defined term in psychopathologic literature. Pathologic sexual excitement implies a general stirring up of sexual strivings; i. e., repressed as well as conscious desires may become obvious to the patient. There emerge desires which to the normally functioning personality are inacceptable, as well as those which are completely acceptable. With acceptable desires there may be emotions which accompany their frustration; with inacceptable desires, emotions which are the outgrowth of ethical conflicts. It is therefore to be expected that anxiety, fear, tension and resentment may be present during a sexual excitement. Pathologic sexual excitement presents an involved and intense emotional reaction and is different from normal sexual excitement, which anticipates the possibility of satisfaction or leads to actual fulfilment of the desires.

CORRELATED PSYCHOPATHOLOGIC AND PHARMACOLOGIC FINDINGS

As has been pointed out in a previous publication,[1] two well defined alterations in the rhythmic contractions of the rabbit intestine were observed—a brief depression and reduction of the amplitude (similar to the influence of epinephrine) and a prolonged elevation of the base line (resembling the changes produced by cholinergic drugs). In the presence of both factors, a contracted and elevated type of curve may occur. If one of these two factors dominates, the expression of the other factor may appear less distinct than that which would correspond to the true intensity.

The curves to be presented in this paper were selected from a large number of observations on psychiatric patients and well persons to demonstrate the influence of various emotions. It should be kept in mind that distinct emotions are infrequently encountered. A careful study of one dominant emotion usually reveals the presence of less obvious, or minor, emotions. In states of ease, when no disturbing emotions, such as anxiety and tension, were present, no change occurred in the curve when the person's blood was added. (See figure 2, tests 156 and 146-2.)

1. *Anxiety.*—The adrenergic effect was of varying degree, depending on the intensity of the anxiety; the effect in the test was usually brief.

CASE 1.—A 22 year old nurse had consulted a psychiatrist several times because of anxiety reactions and difficulties in concentration caused by her work. The blood was taken at the end of a lengthy therapeutic interview in which considerable anxiety had been stirred up. She appeared anxious, clasping her hands tightly, felt "somewhat anxious" and had anxious "anticipation of the test." The test was performed a few hours before menstruation. (See figure 2, test 131.)

2. *Tension.*—The cholinergic effect was of varying degree, dependent on the intensity of the tension and its duration; the effect in the test was lasting.

CASE 2.—A 40 year old woman had suffered from tension, with difficulty in concentration and depressive moods, for several months.

March 31, 1944: The face was drawn; the body was held stiffly, and she appeared tense. She was irritable and restless and felt "jittery" and tired. There were demonstrable difficulties in passive attention and concentration and mild difficulty in retention. She was disturbed by inacceptable sexual desires. The blood was taken on the fourth day of menstruation. (See figure 2, test 129.)

April 21: The patient looked mildly tense but stated that she felt at ease; she was friendly and cheerful. No thinking difficulties were noticed. She was not menstruating at the time of the test. (See figure 2, test 138.)

April 28-June 9: Three other tests, made over a period of two months, at times of severe, as well as of mild, tension, gave the same results as those just presented. Considering her inability to resign herself fully to a personal problem, mild tension was expected to be present, even when not noticeable. The patient was unwilling to admit the presence of emotions to herself except when they were intense. During these tests the patient was not menstruating.

3. *Tension, Anxiety and Resentment.*—The adrenergic effect of resentment was of varying degree, depending on the intensity of the anxiety; the effect in the test was usually brief.

CASE 3.—A 39 year old man (not a patient) had been for two weeks under considerable strain, feeling increasingly "tense," in trying to find a solution to a difficult personal problem. When questioned more closely on Sept. 15, 1943, he mentioned a marked feeling of anxiety lest he might not find an acceptable solution and expressed resentment toward the person involved. No thinking disorder was noticed (psycho-

logic testing was omitted). The test revealed very marked adrenergic (anxiety and resentment) and somewhat less marked cholinergic (tension) factors. (See figure 2, test 61.)

anxiety lest the test would reveal that he had not been able to adjust to the situation. (He is a perfectionistic, self-reliant person, who reacts readily with anxiety to possible failures.) (See figure 2, test 64.)

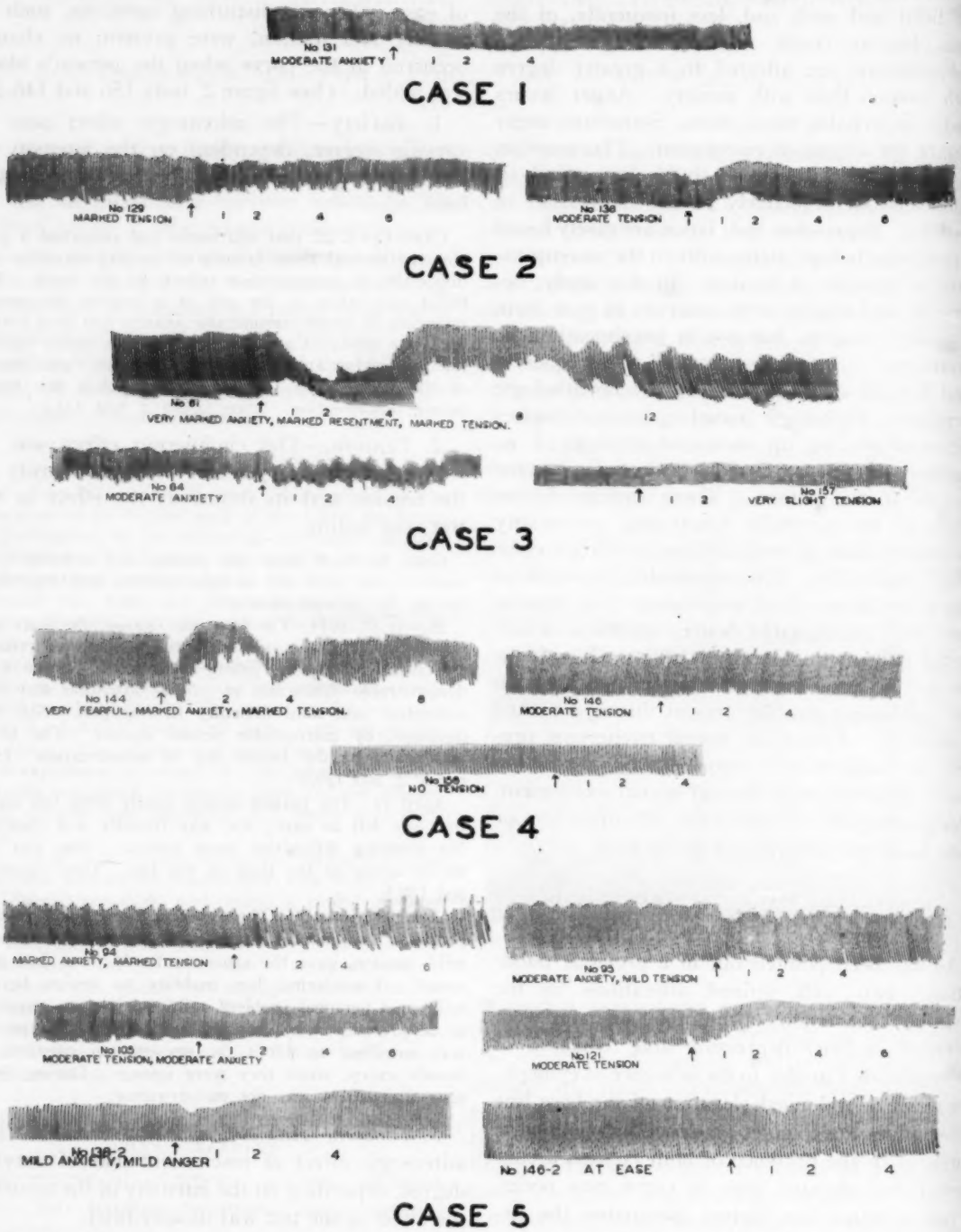

Fig. 2.—Effect on contraction of rabbit duodenum of blood of patients (cases 1 to 5) taken during various emotional states.

The sample of blood was added to the Ringer-Tyrode solution at the time shown by the arrow. The numerals indicate the time in minutes after the addition of the sample of blood.

September 17: An acceptable solution of his problem had been found on the afternoon of September 15. At the time of the test he felt relaxed but experienced

June 16, 1944: Pressure of work had led to his feeling "nervous" and "slightly irritable." His subjective statement was corroborated by the observation of a co-

worker. He appeared slightly tense. (See figure 2, test 157.)

Additional Tests: Four tests, made over a period of nine months, corroborated the previous findings of anxiety being accompanied with adrenergic and tension with cholinergic effects. Resentment was present only in the first test.

4. *Tension, Anxiety and Panic.*—The following case is illustrative.

CASE 4.—In this 46 year old woman there developed a depression with paranoid misinterpretations in January 1944. In April fear became the dominant emotion, accompanied with marked thinking difficulties.

May 3, 1944: With drawn face and rigid posture, the patient looked fearful, saying little. She felt "tired," "tense" and "depressed" and noticed "tightness" in her throat and palpitation. Her hands were moist. She had fearful dreams for several nights. There were subjective observations and objective signs of marked difficulty in concentration. She was not menstruating. (See figure 2, test 144.)

The marked fear (panic) and anxiety state subsided within three days. The patient remained depressed during the six week period of this investigation, but varying degrees of anxiety and tension persisted.

May 10: The patient appeared cheerful and friendly but tense. She felt "restless" and showed definite thinking difficulty (poor passive attention and difficulty in prolonged concentration). She was not menstruating. (See figure 2, test 146.)

June 14: The patient was pleasant; no signs of anxiety or tension were present. (See figure 2, test 156.)

5. *Fear, Anxiety, Tension and Sexual Pressure.*—The following case is illustrative.

CASE 5.—A 47 year old man had suffered from phobias for one and a half years. In the last two months pronounced fear and anxiety were present.

Jan. 14, 1944: The patient looked anxious, apprehensive and tense, complaining of fatigue and painful tension in the arms and legs and describing "intense anxiety" and "discouragement" and the fear that he might harm himself or others. There were mild thinking disorders, such as difficulty in concentration and slowness in remembering. (See figure 2, test 94.)

January 17: The patient felt more self confident and was greatly reassured by hospital protection. Occasionally his fears returned; he then noticed "anxiety," and often "tension" of the abdominal muscles. (See figure 2, test 95.)

February 11: The patient's psychotherapeutic progress had been excellent, but in the days preceding the test he was more tense (feeling of tightness in the back of the neck), and on the day of the test he experienced anxiety in connection with the psychotherapeutic discussion. (See figure 2, test 105.)

March 17: The patient was cheerful but complained of "uneasy sensations" in his stomach and sensations of tension in the abdominal muscles. He appeared tense. This tension was related to inacceptable sexual pressure, which he wished to control. (See figure 2, test 121.)

April 21: The patient was cheerful and pleasant. In the last few days he had expressed guilt over sexual desires. Before the test he became mildly angry over a nurse's behavior. (See figure 2, test 138-2.)

May 10: He was pleasant and denied being anxious or tense. (The patient recovered and left the hospital.) (See figure 2, test 146-2.)

6. *Sexual Excitement.*—In the blood of persons who were sexually excited, but not to a pathologic degree and without anxiety-producing factors, the adrenergic and cholinergic substances were absent in the test.

CASE 6.—This patient, a 26 year old woman, presented pathologic sexual excitement with various strong emotions. Within seventy-two hours after her first delivery, there developed marked excitement, characterized by elation, flight of ideas and intense sexual desire (overt masturbation, heterosexual aggression and, at times, fear of homosexual assault). Her emotions varied in type and intensity, outstanding among them being elation, fear, anxiety, anger and resentment.

Sept. 14, 1943: Intense sexual excitement, with fear and suspiciousness, was present. The patient was resentful toward the nurses. There was no elation. The thinking disorder was expressed in vagueness and irrelevancy. She was not menstruating. (See figure 3, test 59.)

September 17: The patient showed marked excitement, being noisy, resistive and assaultive. She was occasionally fearful, suspicious, mildly resentful and irritable. She appeared distressed and tense, her mood changing readily to elation with flight of ideas. She was erotic toward men and women, exposing herself and making sexual advances. She was not menstruating. (See figure 3, test 65.)

November 30: The patient was mildly elated and slightly irritable (mild tension) and felt somewhat insecure (mild anxiety). She was not menstruating. (See figure 3, test 82.)

7. *Anger, Anxiety and Tension.*—The adrenergic effect of anger was of varying degree, depending on the intensity of the emotion; the effect in the test was usually brief.

CASE 7.—A 30 year old woman (not a patient), reserved and conscientious, reacted readily with mild anxiety to situations in which she felt exposed.

Feb. 23, 1944: For two weeks she had been under considerable tension, being unable to solve a personal problem. For the last hour before the test there was anxiety as to what the test might reveal. The test was made on the third day of menstruation. (See figure 3, test 112.)

March 15: The subject was cheerful and at ease. She was not menstruating. (See figure 3, test 119-1.)

June 2: Resentment had been present for twenty-four hours, with anger one-half hour before the test. She was not menstruating. (See figure 3, test 152.)

8. *Pathologic Elation.*—In the patients studied, pathologic elation always presented an involved emotional reaction because other emotions, of varying intensity, were present (especially tension, resentment and anger, but also fear and anxiety).

CASE 8.—A 57 year old woman was mildly elated, demonstrating overactivity and overtalkativeness (hypomanic reaction). She appeared insecure and at times seemed to hide anxiety.

Jan. 24, 1944: The patient was elated ("felt fine"); she was pleasant but at times expressed resentment toward being considered sick. She was not menstruating. (See figure 3, test 97.)

Case 9.—A 50 year old woman was elated ("felt fine"), overactive and overtalkative, with flight of ideas; she showed marked distractibility and was pleasant but easily angered. She had recovered from three previous manic excitements, which were followed by depressions.

May 31, 1944: The patient was pleasant and overactive and talked incessantly during the test, with marked distractibility and flight of ideas. She said she felt "fine" but was "tense." She was easily angered by the nurses, but there was no indication of resentment. She was not menstruating. (See figure 3, test 150.)

June 2: She was pleasant and overactive and talked incessantly, but with less distractibility and no flight of ideas. She said she felt "fine" and denied feeling tense. She was not angered by the nurses. She was not menstruating. (See figure 3, test 151.)

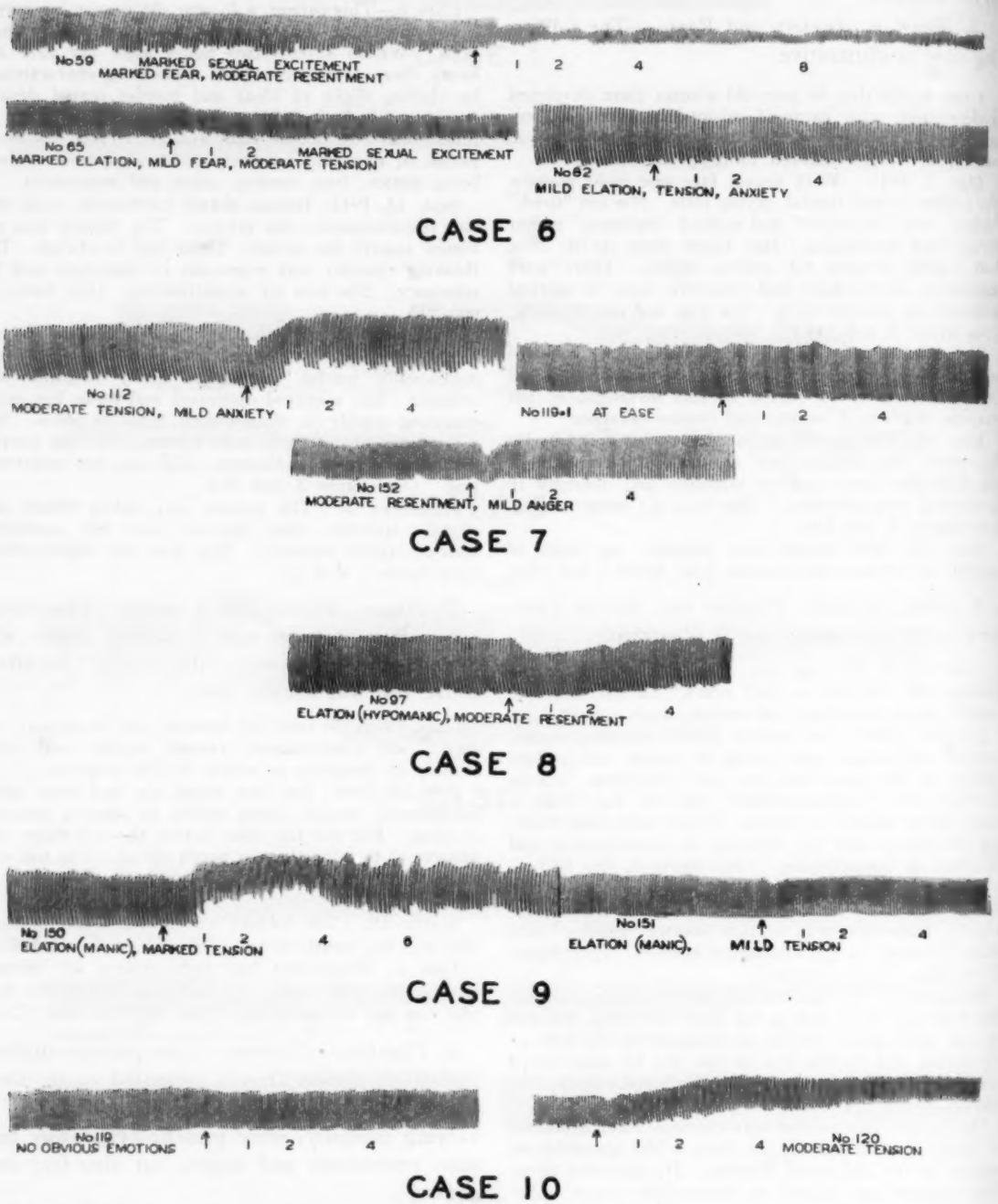

Fig. 3.—Effect on contraction of rabbit duodenum of blood of patients (cases 6 to 10) taken during various emotional states. The records were obtained with the same method as the records shown in figure 2.

9. *Freeing of Affect Under Influence of Sodium Amytal.*—In many psychopathologic conditions

emotions may not seem to play a role. Under the influence of sodium amytal these emotional reactions can become active. This experimental observation is not essentially different from the freeing of affect which occurs under successful psychotherapy. This freeing of emotions and the resulting influence on substances in the blood were observed in 3 patients.

CASE 10.—A 30 year old man had been deeply depressed for several months. He was usually pleasant. He looked sad but denied having any definite emotional reactions. When asked about specific life situations which were known to have been disturbing, he reacted with little emotion.

March 15, 1944: The patient was seen by his physician at 10:30 a. m. He discussed without emotional display an automobile accident and his suicidal attempt a few months previously. Blood was taken at 10:44 a. m. (figure 3, test 119). At 11:15 a. m. he received sodium amytal intravenously. The discussion of the same topics was resumed at 11:30 a. m. The patient remained pleasant but appeared tense and slightly irritable, and to both situations he expressed a slight feeling of guilt but with lack of corresponding emotional display. Blood was taken at 12:16 p. m. (figure 3, test 120).

CONCLUSIONS AND SUMMARY

The experiments presented here demonstrate that during some specific emotions the blood contains factors that can produce effects on the isolated duodenum of the rabbit similar to those of epinephrine and acetylcholine. The physical condition of all the persons studied was good. Menstruation did not seem to influence the reactions.

The results of such experiments are frequently difficult to analyze because one may not be dealing with merely the one emotion which dominates the psychologic and psychopathologic picture. Emotions which are not obvious may have to be considered. Anxiety, resentment and anger are accompanied with definite adrenergic factors; tension, and possibly fear, with cholinergic factors. The blood of one patient in a depressed state with no other emotions detectable had an entirely negative effect during one observation. In other studies of depressed states and in all observations on elated states, anxiety, tension or fear was present, with corresponding adrenergic and cholinergic effects. There does not seem to be an essential difference between normal and psychopathologic emotions except in the intensity of the adrenergic and cholinergic response. The intensity of the response depends on the intensity of the emotion, and probably on individual physiologic capacity to respond.

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EFFECTS OF TRANSIENT STRETCHING OF PERIPHERAL NERVE

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Reports of nerve injuries resulting from war wounds frequently include evidence of damage to peripheral nerves without loss of anatomic continuity. A spindle-shaped neuroma is frequently reported in such circumstances.[1] In other cases a lasting loss of excitability of the nerve is traced to a region of intraneural thickening or fibrosis. Similar findings are encountered in cases of traction injury to the brachial plexus in civilian practice.[2] The condition is usually attributed to intraneural hemorrhage immediately following injury and its replacement by fibrosis.[2] Such cicatrices have usually a very poor prognosis for recovery of function, though occasionally remarkable recovery may occur spontaneously. In attempting to ascertain the features which enable good recovery to be made through some "spindle neuromas" and the factors which prevent recovery in others, we have studied the effect of percussion of nerve experimentally.[3] Percussion will produce with regularity a pseudoneuroma, or localized bulge on the nerve associated with either transient partial paralysis or complete paralysis and peripheral degeneration, according to the intensity of the process. In the most severe degree, however, regeneration was rapid and complete and residual fibrosis minimal in amount. The only hint of more severe complication was the occasional rupture of the perineurial sheath, which was accompanied with some herniation of the nerve bundles, with consequent loss of nerve fibers at this point. We were unable to induce by this means the dense intraneural fibrosis commonly encountered by the neurosurgeon. On the other hand, we also found that with gentle kneading of a nerve trunk a severe intraneural hemorrhage could be induced, and that within limits this could be rapidly resolved, with return of function within a few days or after due regeneration. Intraneural hemorrhage could not therefore per se lead to fibrosis. We then turned to study the different mechanism of stretching injury to nerve, in search of the event leading to fibrosis.

In view of the great distortion of soft tissues produced by the passage of a projectile through them, the possibility of sudden longitudinal stretch appears likely. The experiments of Black and associates,[4] in which blocks of gelatin and the muscles of an animal limb were shown to undergo wide expansion and contraction for many milliseconds after passage of the projectile, indicated the presence of powerful and extremely rapid tensions far beyond the limits of the small ultimate track of the projectile. Such rapidity of tension is difficult to reproduce experimentally without other damage, and the present report is concerned with the effects of a steady pull for some five to ten seconds exerted by the firm grasp of the gloved fingers of the operator.

Previous reports on the histologic and functional disorder resulting from stretch are scanty. Late in the last century nerve stretching was widely used in the treatment of neuralgias of various types, chiefly owing to some physiologic evidence (Sheving, and Debove and Laborde, cited by Takimoto[5]) that stretching of normal nerves injured sensory conduction before motor conduction. It is probable that the differential effect was the result of damage to nerve roots or to the spinal cord. Vogt,[6] Stintzing[7] and Fenger and Lee[8] reviewed the indications for

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1. Tinel, J.: Nerve Wounds, translated by F. Rothwell and C. A. Joll, London, Baillière, Tindall & Cox, 1917. Seddon, H. J.: Three Types of Nerve Injury, Brain **66**:237, 1943.

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3. Denny-Brown, D., and Brenner, C.: The Effect of Percussion on Nerve, J. Neurol., Neurosurg. & Psychiat. **7**:76, 1944.

4. Black, A. N.; Burns, B. D., and Zuckerman, S.: An Experimental Study of the Wounding Mechanism of High-Velocity Missiles, Brit. M. J. **2**:872, 1941.

5. Takimoto, B.: Ueber die Nervendehnung: Experimentelle und klinische Untersuchung, Mitt. d. med. Fak., Tokyo **16**:73, 1916.

6. Vogt, P.: Die Nerven-Dehnung als Operation in der chirurgischen Praxis, Leipzig, F. C. W. Vogel, 1877.

7. Stintzing, R.: Ueber Nervendehnung: Eine experimentelle und klinische Studie, Leipzig, F. C. W. Vogel, 1883.

8. Fenger, C., and Lee, E. W.: Nerve Stretching, J. Nerv. & Ment. Dis. **8**:263, 1881.

the procedure and the methods employed. Vogt [6] also cited animal experiments and described the extravasations of blood in the epineurium induced by stretching. He noted the tortuous vessels and anastomoses which remained. Witkowski,[9] in 1881, described changes in the myelin sheath of nerve fibers, consisting of a widening of the incisures of Schmidt and Lantermann immediately after stretching and degeneration, more marked in the periphery of the nerve bundles, if an interval of survival was allowed (rabbit, guinea pig). Traction was exerted by pulling the nerve with a hook. Weir Mitchell [10] observed that the sciatic nerve of a rabbit could be stretched "until the lengthening was equal to three-fourths of an inch in three inches" before motor conduction failed.

Takimoto [5] reviewed the whole subject of nerve stretching as a surgical treatment and cited both animal experiments and human cases. He noted the enormous weight (approximately 32 Kg.) necessary to stretch the human sciatic nerve. Tillaux [11] had earlier observed that a weight of 54 to 58 Kg. was necessary to rupture the nerve. Takimoto used weights of 100 to 400 Gm. attached to a sling to stretch the sciatic nerve of rabbits. Hemorrhages in the nerve were not a necessary part of the lesion and were sometimes absent with extensions as great as 750 Gm. When hemorrhages occurred, they were usually in the epineurium. Few occurred within the perineurium. The striking immediate change was either the breaking up of axis-cylinders into short segments or thinning at regular intervals so as to produce beading. The Schmidt-Lantermann incisures on the myelin sheaths widened, and rupture occurred at these points. If survival was allowed for periods of six to forty-eight hours, the nerve became edematous, and droplets of myelin were found near the nodes of Ranvier. Degeneration of myelin sheaths began after three days and was more severe in the periphery of the nerve bundle. If the stretch was not severe, motor function was less affected than sensory, and a return of motor function could be observed in as brief an interval as twelve minutes. In the clinical cases cited there was no relief of referred pain, and the procedure was not recommended for the abolition of this type of pain. Sections from human nerves confirmed the beading of axis-cylinders in the region of nerve stretched.

The widening of the incisures of Schmidt and Lantermann produced by stretching was noted also by Glees,[12] who examined the phenomenon in fresh fibers under polarized light. He concluded that these structures are a mechanism permitting extension of nerve fibers.

9. Witkowski, L.: Zur Nervendehnung, Arch. f. Psychiat. **11**:532, 1881.

10. Mitchell, S. W.: Injuries of Nerves and Their Consequences, Philadelphia, J. B. Lippincott & Co., 1872.

11. Tillaux, P.: Des affections chirurgicales des nerfs, Thesis, Paris, P. Asselin, 1866.

METHOD

The very rapid longitudinal stretch of nerve that must occur in injuries produced by projectiles and also in the more usual violence of civilian accidents is extremely difficult to reproduce experimentally in uncomplicated form. Traction on a nerve with a hook, as used by earlier investigators, has the disadvantage that the situation of first injury is unknown, and may often be the nerve roots. We have therefore used the procedure of grasping the nerve as gently as possible between the fingers of two hands and stretching a known segment. The tension applied was not measured, but in all later experiments the lengthening of the nerve was gaged by first applying loose ligatures at measured intervals and then measuring the intervals after stretch. This method is only approximate, for sometimes the nerve would give under the fingers and not at the place expected. The procedure was carried out on cats at open operation, with the animal under deep pentobarbital anesthesia. After the first few experiments the nerve used was the peroneal.

OBSERVATIONS

Effect of Stretch on Sciatic Nerve.—The sciatic nerve of the cat, exposed at operation with the animal under pentobarbital anesthesia, proved to be difficult to stretch without injury to the nerve at the points at which force is applied. The most satisfactory method was found to be by hooking the nerve between gloved fingers of each hand and pulling in opposite directions. The tension required to elongate the nerve in any appreciable degree was considerable, and it was inevitable that some of the tension was directed to the central and peripheral attachments of the nerve. Our attempts to stretch this nerve were abandoned after 2 experiments, in which petechial hemorrhages appeared over a length of 2 cm. in one and of 4 cm. in another, after a maximum effort had been made to elongate the main trunk of the nerve. In neither instance was any weakness of plantar flexion or dorsiflexion of the foot or of spreading of the toes observed twenty-four hours after the operation. Appreciation of touch and pinch to the foot appeared to be intact.

The animal was allowed to survive for nine days in each experiment. In the nerve which

12. Glees, P.: Observations on the Structure of the Connective Tissue Sheaths of Cutaneous Nerves, J. Anat. **77**:153, 1943.

initially had shown epineurial hemorrhage over a length of 2 cm., the epineurial vessels were all tortuous, and one small arteriole was found to be thrombosed. The epineurial fibroblasts were more prominent than usual and appeared to have been activated by the trauma. The nerve bundles showed no degeneration, but several changes were observed in the Schmidt-Lantermann incisures.

On the side on which more extensive initial epineurial hemorrhage had been present, a number of ruptured vessels were found, one small fasciculus was degenerated and patchy edema was found in another, with swelling of axis-

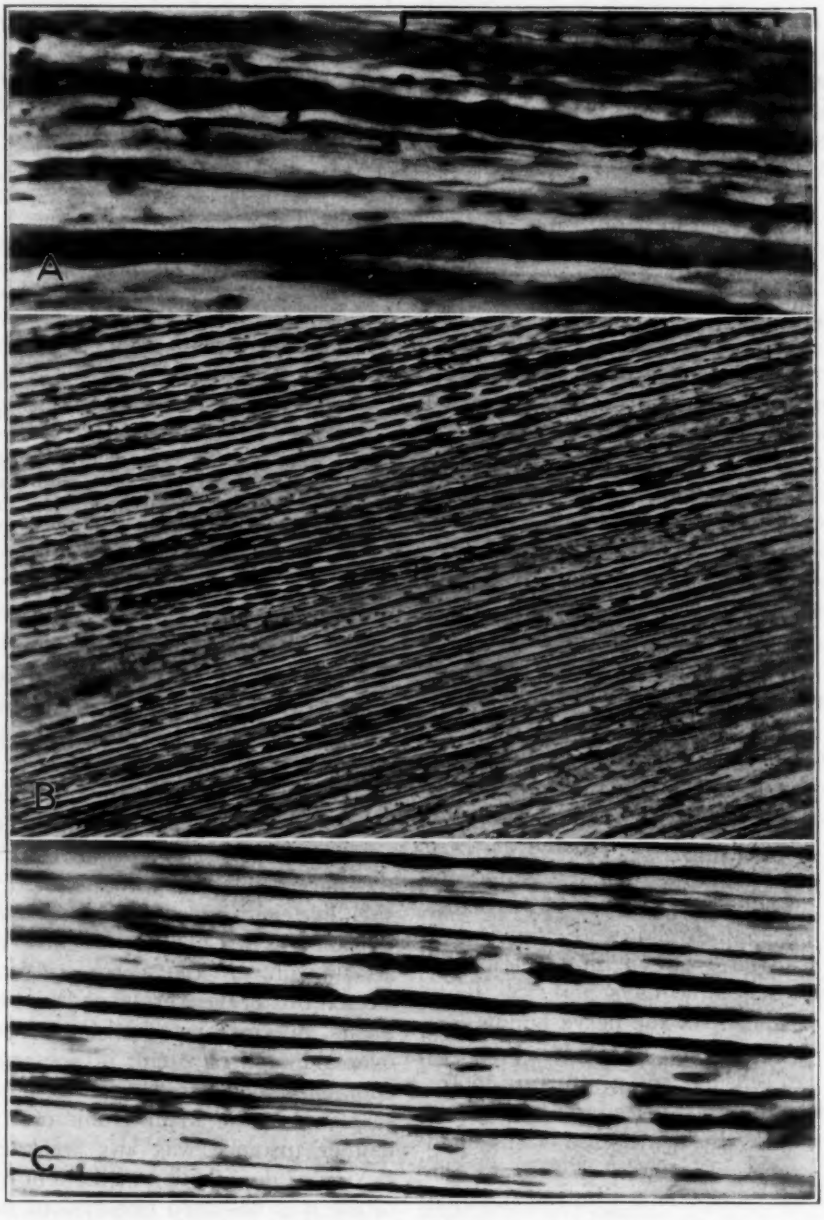

Fig. 1.—*A*, greatly swollen, but otherwise intact, axis-cylinders in an edematous segment of sciatic nerve nine days after stretching. The ruled line in the upper right corner corresponds to 0.1 mm. Gros-Bielschowsky method. *B* (experiment 3, table), beading and swelling of axis-cylinders in peroneal nerve twenty-eight days after stretching, with partial recovery of motor function. *C*, higher magnification of beading of axis-cylinders.

bundles were edematous over an extent of 5 to 10 mm. and in this area showed remarkable swelling of the axis-cylinders (fig. 1 *A*). The myelin was swollen and slightly irregular. No cylinders. With the edema on both sides was some proliferation of endoneurial cells, with a few mononuclear histiocytes. There was no beading of axis-cylinders or myelin.

These changes are consistent with patchy partial ischemia of the nerve and were identical with those found by us [13] after ligature of the vessels of the sciatic nerve, with which the free longitudinal vascular anastomosis allows only minimal edematous reaction. It would appear that the effort to stretch the nerve had resulted in rupture of a small epineurial vessel, with minimal consequences.

We therefore turned to more slender nerves.

Effect of Stretch on the Peroneal Nerve.—By section of the biceps femoris muscle of the cat near its insertion and reflection of the lower portion of the muscle posteriorly, the peroneal nerve, from its origin from the sciatic nerve to its disappearance into the pretibial muscles, can be exposed. Ligature and section of some vessels passing between the popliteal space and the biceps muscle are necessary to expose it completely throughout its course. The nerve can be freed throughout its length without damage to its blood supply, which enters at the ends. Loose ligatures were applied to the nerve, and the distance between them was measured before and after stretch.

When stretch is applied with the gloved fingers, the peroneal nerve is felt to extend moderately easily, in the manner of a plastic material, so that with little force its length can be doubled. On release it remains near the new length and lies in redundant folds. The increase in length occurs about the middle of its course, and more commonly in its proximal than in its distal half.

Altogether, 10 experiments of this type were carried out, with varying degrees of stretch and varying durations of survival, from five to one hundred and forty days. Three other experiments were made on small cutaneous nerves, such as the sural. The immediate consequences of a single stretch applied in this manner were simple lengthening, epineurial hemorrhage or partial rupture of the sheath. On no occasion was stretching carried to the point of complete rupture. These consequences will be dealt with separately.

Data on Ten Experiments Showing Effects of Transient Stretch of Peripheral Nerve

Experiment No.	Original Interval, Mm.	Interval After Stretch, Mm.	Immediate Pathologic Change	State After 24 Hours	Onset of Recovery, Days	Duration of Complete Recovery, Days	Duration of Experiment, Days	Motor Conduction at End of Experiment	Histologic Changes
1	31	49	Nil	Severe weakness	1	12	13	Full	Patchy edema, beading, microscopic hemorrhage
2	6	13	Nil	Paralysis	3	28	28	Full	Patchy edema, beading, regeneration
3	6	25	Nil	Paralysis	3	Incomplete	28	Fair	Patchy edema, beading, small areas of regeneration
4	10	20	Nil	Paralysis	12	31	75	Full	Edema, regeneration, some occluded epineurial arterioles
5	10	? 20	Nil	Weakness	1	14	140	Full	Beading in periphery of some fasciculi
6	12	33	Small epineurial hemorrhage	Paralysis	41	64	75	Full	Edema of all fasciculi; some occluded small epineurial vessels; regeneration
7	30	43	Small hernia	Paralysis	..	..	5	Nil	Small rupture of perineurium; thin limiting membrane remaining; congestion of endoneurial vessels
8	31	46	4 mm. hernia	Paralysis	..	..	5	Nil	Swelling showed rupture of perineurium; thrombosed epineurial vessels; loss of axons and myelin in and above swelling
9	30	54	Large hernia	Paralysis	..	..	13	Nil	Large fibroblastic mass infiltrating muscle, proximal and distal necrosis of nerve
10	10	? 20	Small hernia	Paralysis	21	48	140	Full	Pseudoneuroma with almost perfect regeneration

It was at first remarkable that the peroneal nerve could be stretched until the distance between markers on it increased 100 per cent, often without any sign of hemorrhage, and with only slight weakness twenty-four hours later, when the animal had recovered from anesthesia. Recovery of apparently full power of dorsiflexion of the foot and spreading of the toes occurred within fourteen days. We did not attempt to define the sensory disturbance.

In experiments 1 and 5 (table) restoration of both function and structure appeared to be complete after the interval indicated, except that the larger axis-cylinders appeared swollen and had a segmented appearance in some of the nerve bundles (fig. 1 *B* and *C*). Such segmentation was usually more prominent at the periphery of the nerve bundle. The myelin appeared to

13. Denny-Brown, D., and Brenner, C.: Paralysis of Nerve Induced by Direct Pressure and by Tourniquet, Arch. Neurol. & Psychiat. **51**:1 (Jan.) 1944.

be of normal structure, though it was occasionally beaded. Each node was noted to be heavily stained.

A stretch of over 100 per cent (experiments 2, 3, 4 and 6) induced occasionally immediate small, petechial epineurial hemorrhages. The nerve appeared pale and thin. Complete paralysis was present after twenty-four hours. Recovery of function occurred progressively and was complete in about one month except when epineurial hemorrhage had occurred. In this case regeneration was also found to be complete, but more obvious histologic changes remained. The nerve bundles were often edematous, with widely distended perineurial spaces, as in figure 2 *D* and *E*. The neural fibroblasts had proliferated so that the endoneurium was more cellular and stained slightly more intensely for collagen

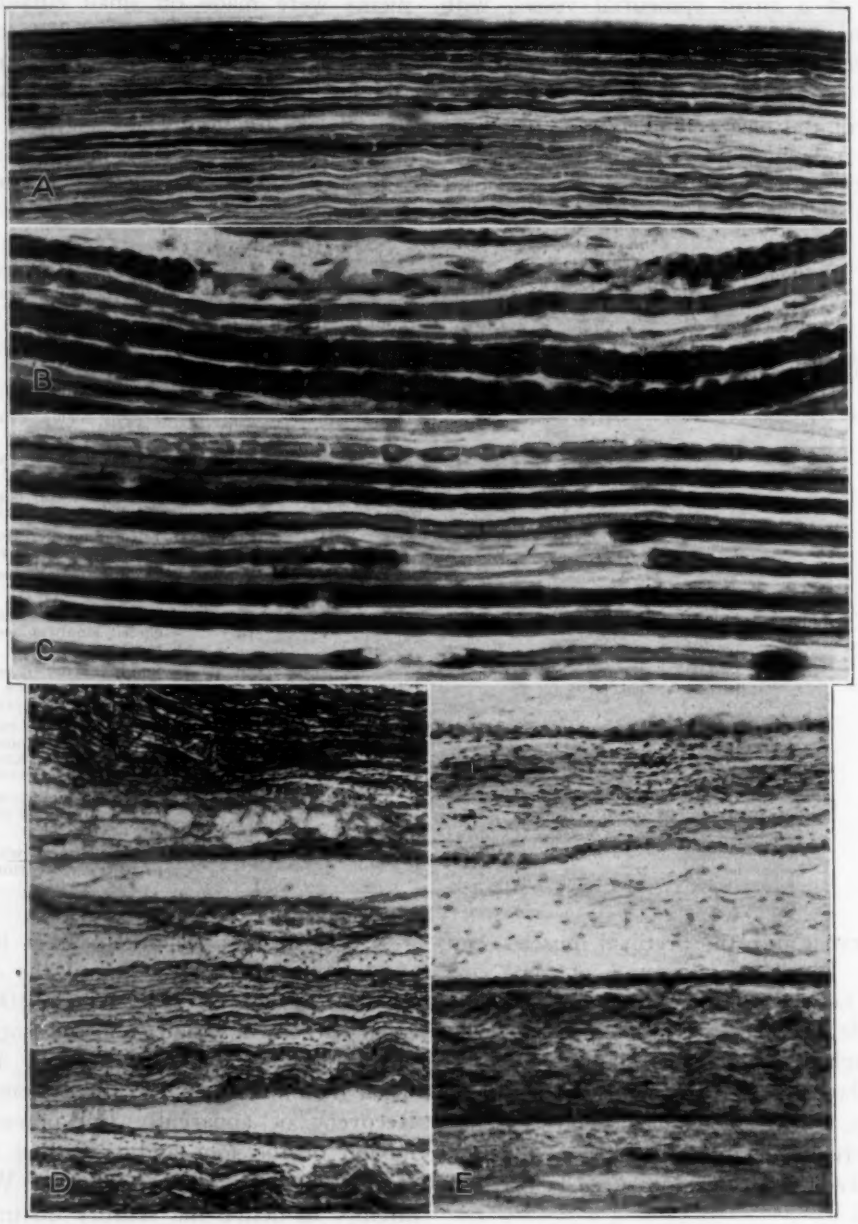

Fig. 2.—*A*, peroneal nerve one hundred and forty days after stretch, showing the numerous regenerated, thin myelin sheaths; Spielmeyer stain for myelin. *B*, same nerve as that presented in *A*, showing gap in myelin sheath in an undegenerated fiber; sudan III and hematoxylin stains. *C*, fiber similar to that presented in *B*, showing other types of gaps in the myelin sheath and beading of myelin; Spielmeyer stain for myelin. *D*, peroneal nerve (experiment 1, table), showing edema of the neural fasciculus in the center, as compared with an unaffected fasciculus above; Gros-Bielschowsky stain. *E*, peroneal nerve (experiment 4), showing edema of a fasciculus seventy-five days after stretching; hematoxylin and eosin stain.

than the unaffected bundles. Many of the nerve fibers had the thin myelin of regeneration (fig. 2*A*). The original areas of damage to nerve fibers were seen as patchy distention of the nerve bundle with fluid, with moderate increase in neural fibroblasts, and interpreted as neural edema. The more severe and prolonged the initial paralysis, the more extensive was the subsequent edematous change. In experiment 6 (table) all the fasciculi of the nerve were then involved throughout their extent. The perineurium over such bundles was slightly thickened

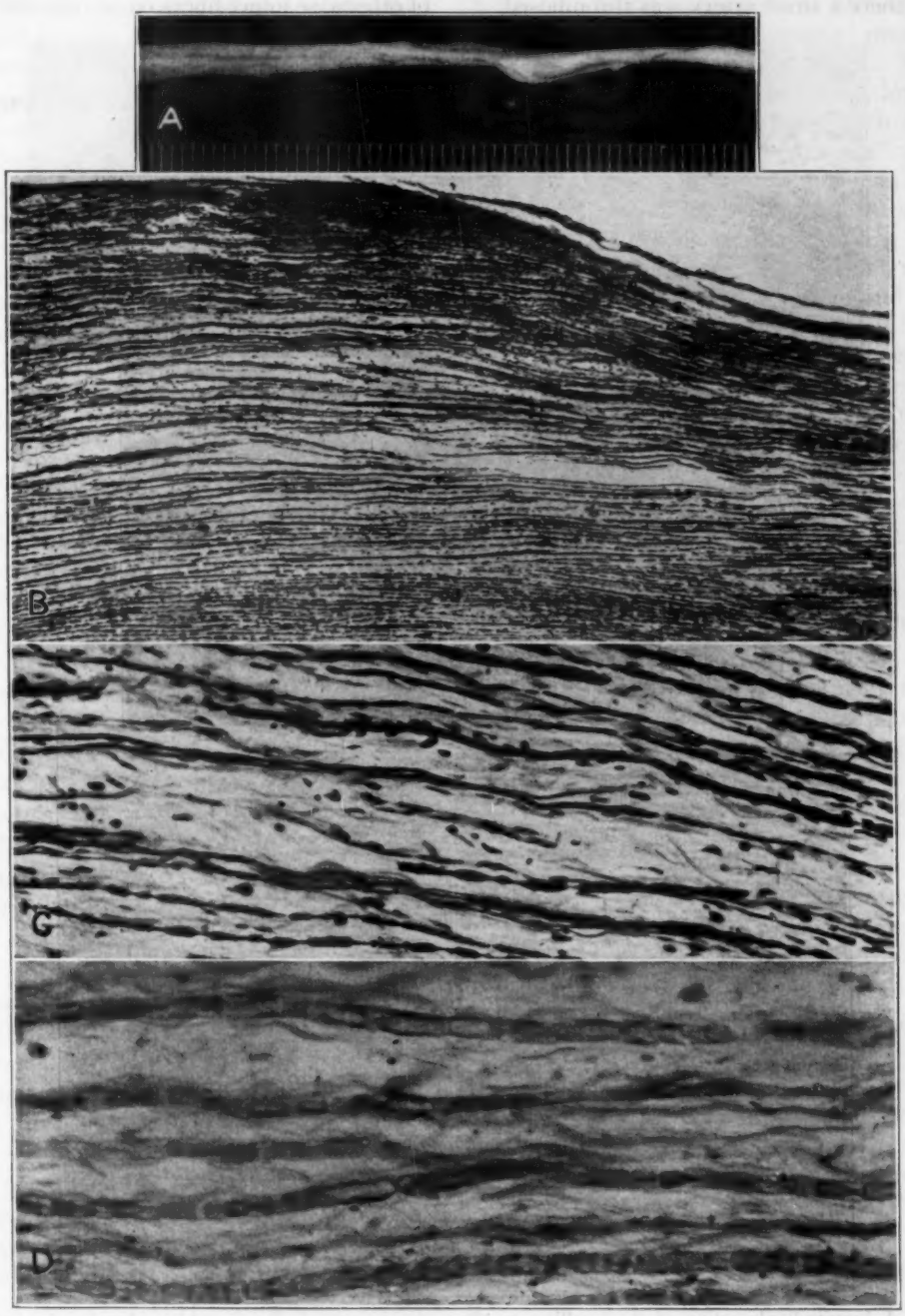

Fig. 3.—*A*, "pseudoneuroma" in the peroneal nerve one hundred and forty days after formation of a small hernia. The proximal end of the nerve lies to the left. The scale is in millimeters. *B*, distal side of the pseudoneuroma shown in *A*. Gros-Bielschowsky–cresyl violet method. *C*, section of field shown in *B*, with higher magnification. *D*, from same field as that shown in *C*, with phosphotungstic and hematoxylin stain (Mallory).

in places but was otherwise intact. The epineurium showed increase of young fibroblasts in some areas and a notable dilatation of all the veins. Some of the arterioles had greatly thickened walls and proliferation of the intima, and here and there a small artery was thrombosed.

was also found, but this was not prominent. The degeneration was directly related to vascular damage in the epineurium. That it was essentially ischemic in nature was shown by the frequent finding of large gaps in the myelin sheaths of otherwise intact fibers on or near the degenera-

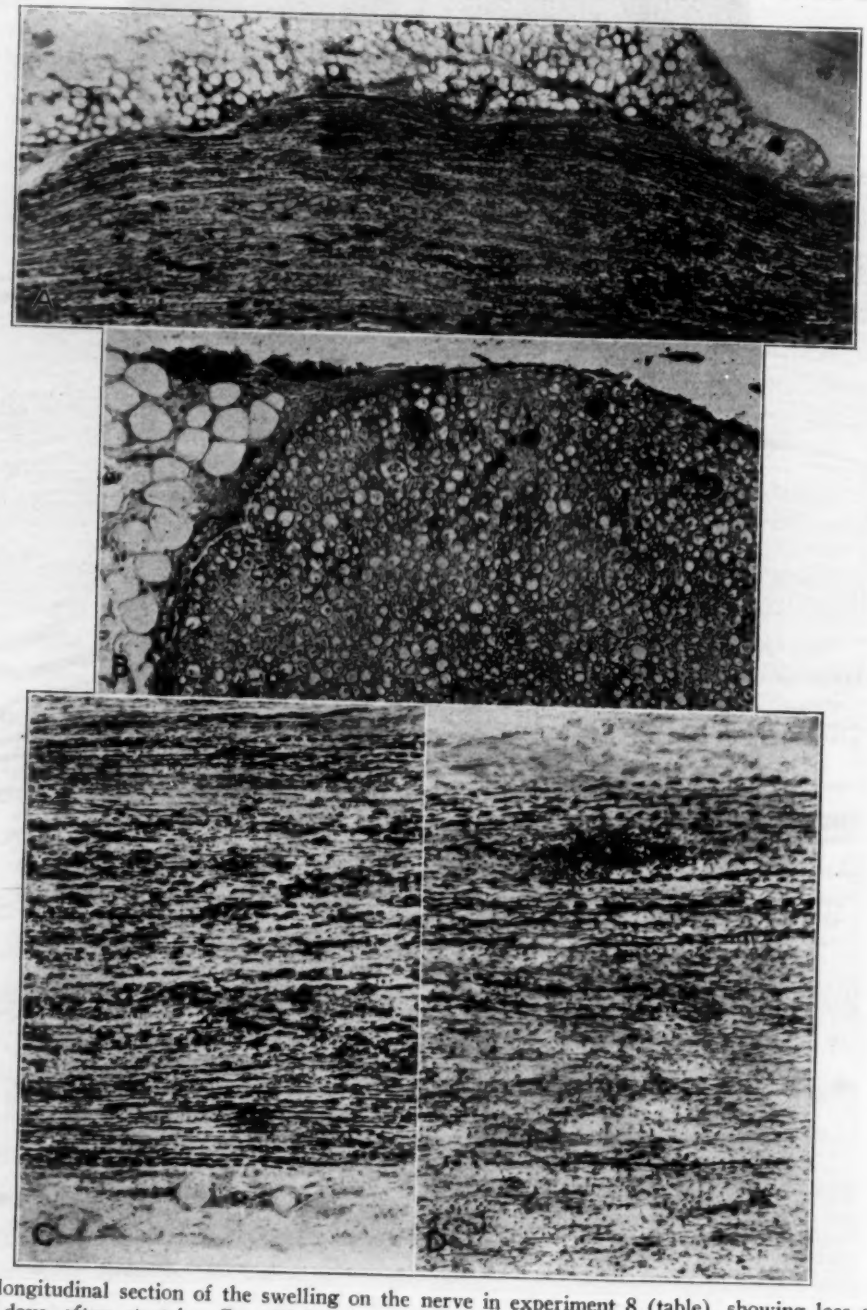

Fig. 4.—*A*, longitudinal section of the swelling on the nerve in experiment 8 (table), showing loss of structure in center five days after stretch; Gros-Bielschowsky–cresyl violet stain. *B*, transverse section of small swelling five days after stretch (experiment 7); phosphotungstic acid hematoxylin stain. *C*, peroneal nerve just proximal to the swelling shown in *A*, showing loss of structure in center and beading at edges five days after stretch; Gros-Bielschowsky stain. *D*, peroneal nerve just proximal to swelling thirteen days after stretch (experiment 9).

In some bundles of nerve fibers the beading of axis-cylinders seen in lesser degrees of injury

tive lesion (fig. 2 *B* and *C*). Such myelin gaps were identical with those we have described in

the ischemic lesions produced by compression of nerve.[14]

In such lesions a thin myelin sheath was found to regenerate but the fibers remained in this state for one hundred and forty days in experiment 5. Though some collagenization remained at the site of damage, the condition was not such as to interfere with function.

Pseudoneuroma and Neuroma Produced by Traction.—If tension is continued after an increase in length of 100 per cent is obtained, the nerve does not suddenly rupture. Instead, there is heard a small, sharp noise, which may be described as a "crack" or a "snap," without any notable increase in extensibility. Close inspection of the peroneal nerve to determine the origin of this sound revealed that at one point a small white hernia had appeared on the side of the main nerve bundle. This most commonly occurred at about the junction of the upper and the middle third of the nerve. The herniation was evidently due to protrusion of the white nerve fibers through a longitudinal split in the perineurium. The split varied in length from 2 to 4 mm. There was no hemorrhage. If tension was persisted in, the whole nerve bulged out of the sheath at this point and the sheath threatened to rupture, becoming progressively thinner and slipping to one side of the nerve bundle. Further tension will lead to its final rupture, when the nerve fibers then begin to extend, not losing their continuity until long shreds are eventually pulled out.

The point at which the perineurium first ruptures and nerve fibers begin to herniate evidently marks the relief of a high internal tension within the tubular sheath. From that stage onward the resistance of the nerve to extension is much less.

Such an event always led to immediate complete paralysis. The smallest hernia thus obtained was allowed to remain one hundred and forty days. Recovery in function had commenced about the twenty-first day and was complete by the forty-eighth day. Nevertheless, at the end of the experiment a large pseudoneuroma was found on the nerve (fig. 3 *A*). On section this was found to consist of normal and regenerated nerve fibers separated by edematous tissue fluid (fig. 3 *B, C* and *D*). There was a moderate increase of endoneurial fibroblasts, with corresponding strands of collagen (fig. 3 *D*), but, except at the site of perineurial tear, no obstruction to regeneration had occurred. Most of the young regenerated fibers lay close to the former tear in the perineurium, indicating that the original damage to the axis-cylinders had been mainly at this point. Some axis-cylinders had entered the perineurial scar, there forming neuromatous whorls among the fibroblastic tissue. Not more than 2 per cent of fibers had been lost in this way. The condition was that which had been described as the "pseudo-neuroma" following percussion of nerve.[3] Distal to the swelling the nerve was thin for a distance, and in this region there was evidence of damage having occurred to some small epineurial vessels, which were then tortuous and had thickened walls and evidence of recanalization, with phagocytosis of some nearby blood pigment. Here, more nerve fibers had the thin sheaths of regeneration, and the few surviving large myelin sheaths showed gaps in their continuity (fig. 2 *B* and *C*). Edema of the nerve bundles and some beading of the original axis-cylinders, both proximal and distal to the pseudoneuroma and in its substance (fig. 3 *C*), were found.

An early stage of small herniation was also examined (experiment 7, table). The animal was killed on the fifth day. Rupture of epineurial vessels with thrombosis of small arterioles was found in two places in the epineurium left over the bulge. A transverse section (fig. 4 *B*) showed the loss of perineurium, of which one small last layer appeared to remain or to have been regenerated. Myelin sheaths next to the hernia had undergone complete dissolution, but the structure of the nerve remained intact. There was great congestion of the endoneurial vessels next to the opening, with some early proliferation of fibroblasts in this situation.

Section of a similar small hernia found in experiment 1, after thirteen days of survival, showed loss of perineurial structure with proliferation of fibroblasts and regeneration of nerve fibers through the opening (fig. 5 *A* and *B*). Phagocytes loaded with droplets of myelin had also been carried into the epineurium. Though the main bulk of nerve fibers remained intact, the small hernia, less than 1 mm. long, had evidently broken free of all perineurial restraint, with corresponding devastation in neural structure.

More pronounced herniation at the time of stretch induced severe damage to the nerve. In 1 such experiment, in which an opening 4 mm. long in the nerve and almost complete herniation of the contents through the opening had occurred,

14. Denny-Brown, D., and Brenner, C.: (*a*) Lesion in Peripheral Nerve Resulting from Compression by Spring Clip, Arch. Neurol. & Psychiat. **52**:1 (July) 1944; (*b*) footnote 13.

all the nerve fibers and myelin within the bulging hernia were found to be completely necrotic five days after the injury (fig. 4 *A*). The necrosis extended proximally in the center of the nerve trunk for 8 mm., leaving beaded axis-cylinders intact at the edge of the fasciculus (fig. 4 *C*). Throughout this region of damage to nerve fibers, fibroblasts and histiocytes were in active proliferation, and only occasional isolated surviving Schwann cells could be found. In the perineurial sheath in the proximal part of the swelling were an early fibroblastic proliferation and an inflammatory mononuclear and polymorphonuclear reaction.

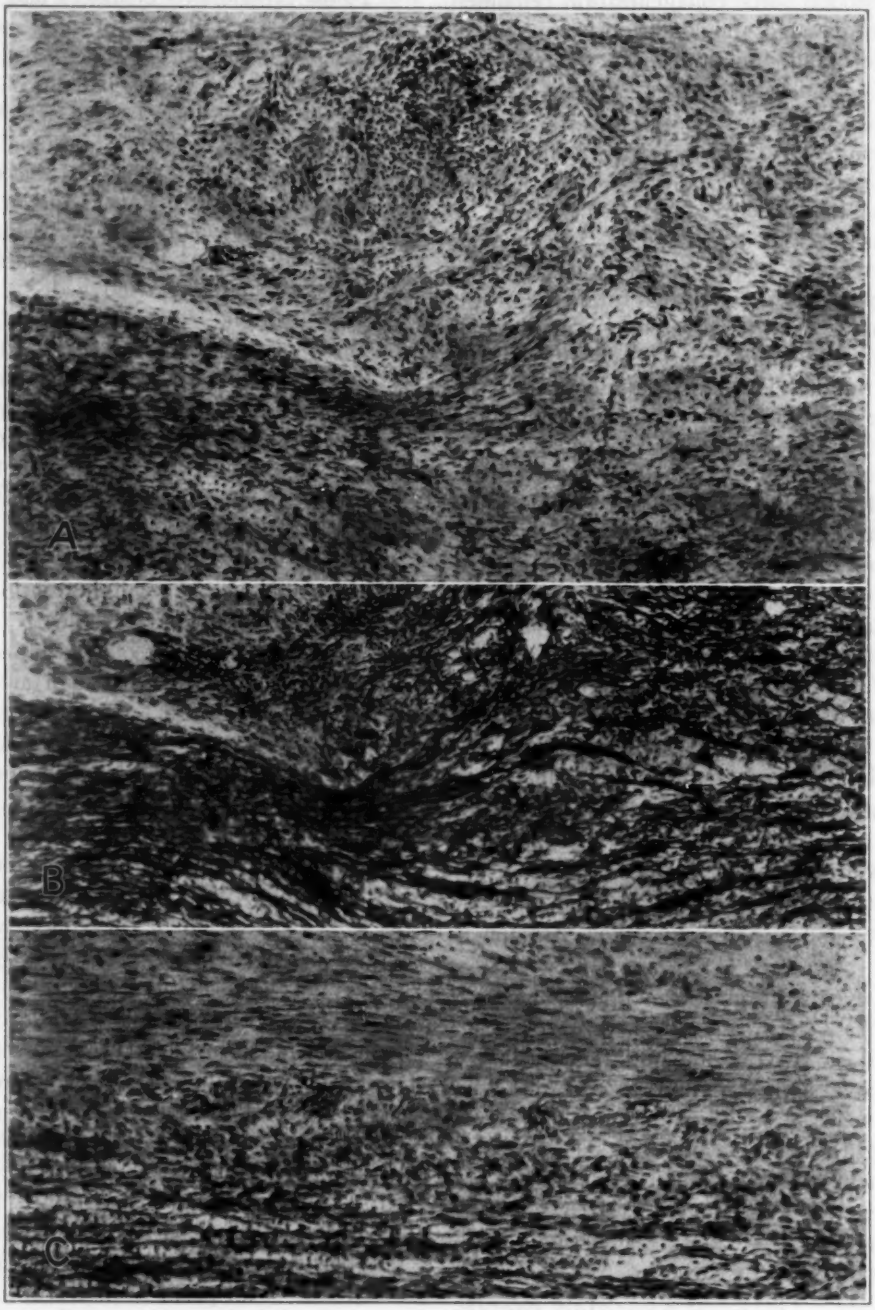

Fig. 5.—*A*, peroneal nerve, upper margin of a herniation through the perineurium thirteen days after stretch. The nerve bundle lies below, the herniated portion to the right. Hematoxylin and eosin stain. *B*, portion of the field shown in *A*; Gros-Bielschowsky method. *C*, perineurium lying between the epineurium (above) and a necrotic neural fasciculus (below). Note small capillaries running vertically between the two. Hematoxylin and eosin stain.

In another experiment a large herniation was allowed to persist for thirteen days before the animal was killed. The swelling here was entirely cellular and contained no trace of axis-destruction of nerve fibers also extended medially in the center of the nerve for over 10 mm. (fig. 4 *D*). The greater number of cells were neural fibroblasts, with oval, pale nuclei and active

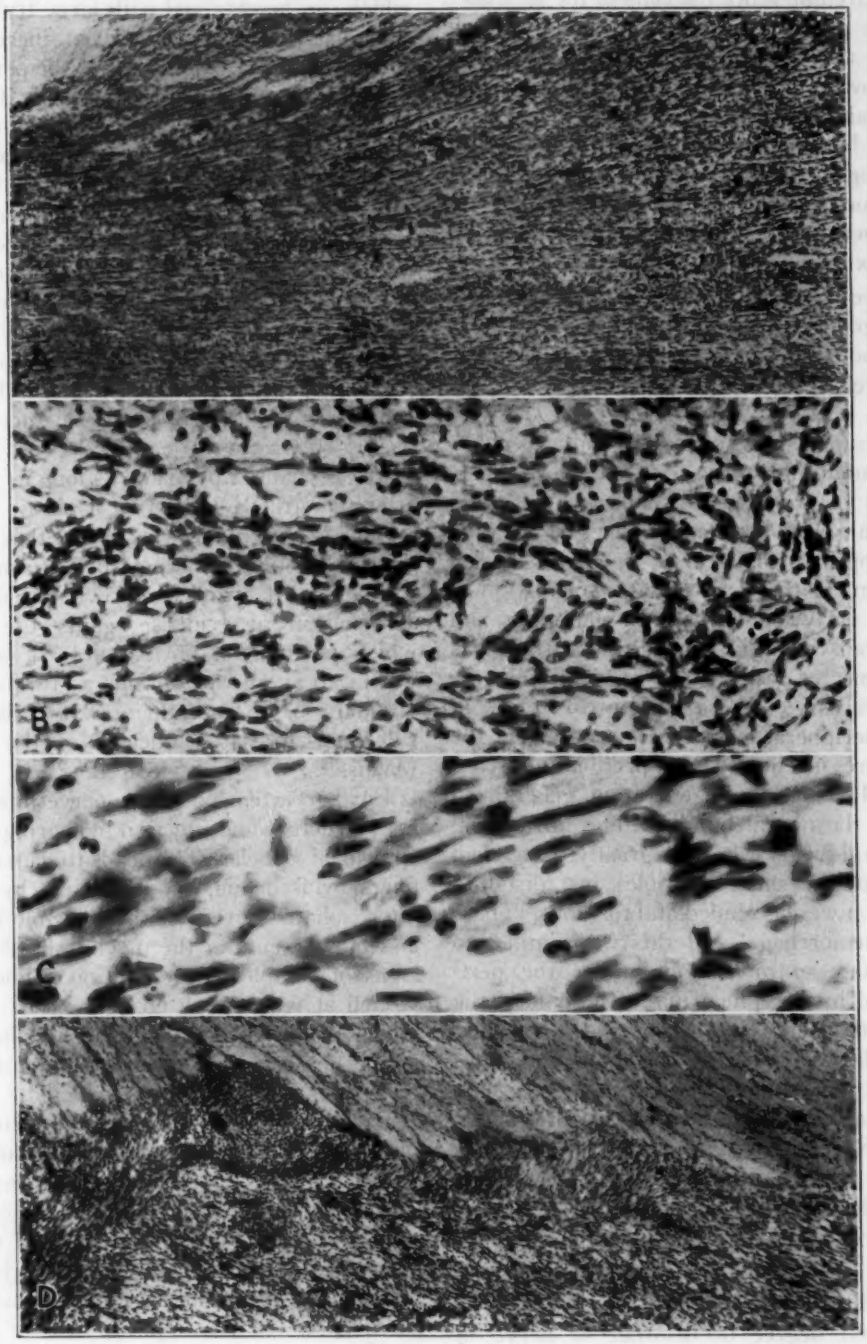

Fig. 6.—*A*, peroneal nerve, upper margin of a swelling thirteen days after injury (experiment 9), showing disappearance of myelin and the small amount of free fat; sudan III and hematoxylin stains. *B*, higher magnification of central part of neuroma shown in *A*, exhibiting loss of pattern; hematoxylin and eosin. *C*, higher magnification, to show nuclear detail and mitoses. *D*, from the same nerve as that shown in *A*, *B* and *C*, illustrating adherence to muscle at the edge of the fibroblastic mass; hematoxylin and eosin stain.

cylinders, and only a few fragments of degenerated myelin remained (fig. 6 *A*). The mitosis (fig. 6 *B* and *C*), and the remainder were fat-filled phagocytes. The phosphotungstic

acid hematoxylin stain, which, as has been shown elsewhere (Denny-Brown [15]), is almost specific for Schwann nuclei, showed only two or three such nuclei in each section. Through three quarters of its circumference the cells of the herniated tissue were proliferating laterally among muscle fibers and the tendon aponeurosis (fig. 6 *D*), unlimited by the perineurium, which existed only in the remaining quarter. The structure of the nerve had been completely lost in this region. The swelling in this instance was therefore identical in structure with the central neuroma of a sectioned nerve, though maintaining direct continuity proximally and distally.

The nerve distal to the neuromatous bulge had also undergone dissolution, though the longitudinal collagenous tubes remained intact. The whole cellular swelling, and the central cone of the nerve just proximal and distal to it, showed complete disappearance of myelin and axis-cylinders, with intense phagocytosis. The more superficial parts of the nerves connected with the swelling, in which beaded fragments of axis-cylinders appear in figure 4 *D*, showed wallerian degeneration, in the form of fatty ovoids. The process of early dissolution of the axon and myelin in the swelling itself and the central parts of the connected nerves appeared to indicate ischemic necrosis of these structures. Only in the most peripheral part of the course of the nerve, before it entered the pretibial muscles, was normal wallerian degeneration generalized throughout the neural bundle. The intraneural and epineural veins were all greatly distended, and many of the small arterioles just distal to the herniation were occluded and tortuous. There was little hemorrhage, and this was limited to small punctate extravasations under the perineurium and in the epineurium. In some of the bundles of the nerve just distal to the swelling small capillaries appeared to enter the perineurium in great numbers (fig. 5 *C*), giving evidence of a collateral circulation to an ischemic segment. Regeneration was active in the segment of the nerve proximal to the swelling, but few fibrils had penetrated to the swelling, and these appeared then to lose direction and wander aimlessly.

This condition may therefore be described as the maximum degree of disorder of nerve in continuity. Though we have not had an opportunity to follow its development for long periods, there can be no doubt that it presents an obstruction to regeneration.

15. Denny-Brown, D.: Importance of Neural Fibroblasts in the Regeneration of Nerve, Arch. Neurol. & Psychiat., to be published.

COMMENT

The experiments that have been cited indicate that the peripheral nerves have some physiologic extensibility. The degree of extension which can be obtained with large trunks, such as the sciatic nerve, is small but increases in the smaller fasciculi. Segments of the peroneal nerve of the cat can extend to nearly 100 per cent of their resting length without damage. With such extensions, some of the larger axis-cylinders become beaded in appearance, and the incisures of Schmidt and Lantermann in the myelin sheath are lengthened. Identical beading can be produced by tension in the dead but unfixed axis-cylinder by longitudinal tension. We have taken precautions to avoid such artefact in the present experiments and would comment only that this phenomenon must have a physical basis, for it can be reproduced in an elastic tube filled with plastic substance.

These changes persisted as long as five months after the stretch, indicating a plastic rather than an elastic structure. We regard this feature and the similar persistence of the deformities of the axon induced by edema previously described [14a] as being strong evidence against the hypotheses which postulate a normal flow of axonic fluid within an axonic membrane, a "turgor pressure" (Young [16]) or reproduction of a basic neural substance near the nucleus of the nerve cell (Weiss [17]).

Further extension of the nerve interferes with both structure and function by tearing the smaller epineurial vessels. This leads to damage to nerve fibers by ischemia, producing patchy edema, or intermediate degrees of the ischemic lesion, with loss of segments of the myelin sheaths, or small areas of complete degeneration. The degree of stretch at which such changes occur is not easy to determine except that petechial hemorrhages in the epineurium indicate that a major degree of the disorder has occurred. The neural degeneration thus produced is recoverable without complication, and no evidence of obstruction was obtained. The level at which damage occurred was not constant and evidently corresponded to some variability in tensile strength of the epineurial fibrous and elastic tissue. The insertion of the nerve into muscle was not found to be a particularly vulnerable point.

Of greater interest was the demonstration that stretching a nerve could produce a swelling in

16. Young, J. Z.: Contraction, Turgor, and the Cytoskeleton of Nerve Fibers, Nature, London **153**: 333, 1944.

17. Weiss, P.: Evidence of Perpetual Proximo-Distal Growth of Nerve Fibers, Biol. Bull. **87**:160, 1944.

continuity, for the causation of such swellings in clinical nerve lesions has been in some doubt. The mechanism of the swelling was traced to an initial rupture of the perineurial sheath, an event which makes its first appearance as a longitudinal split, through which the contents immediately herniate as if under great internal pressure. The degree of herniation determined the subsequent fate of the nerve at this point. The small hernias retained a thin superficial layer, probably a last internal lamina of perineurium, which appeared to preserve the general structure of the neural fasciculus. There was, nevertheless, evidence of damage to endoneurial blood vessels, which became greatly congested at this point. The subsequent course of such a swelling indicated

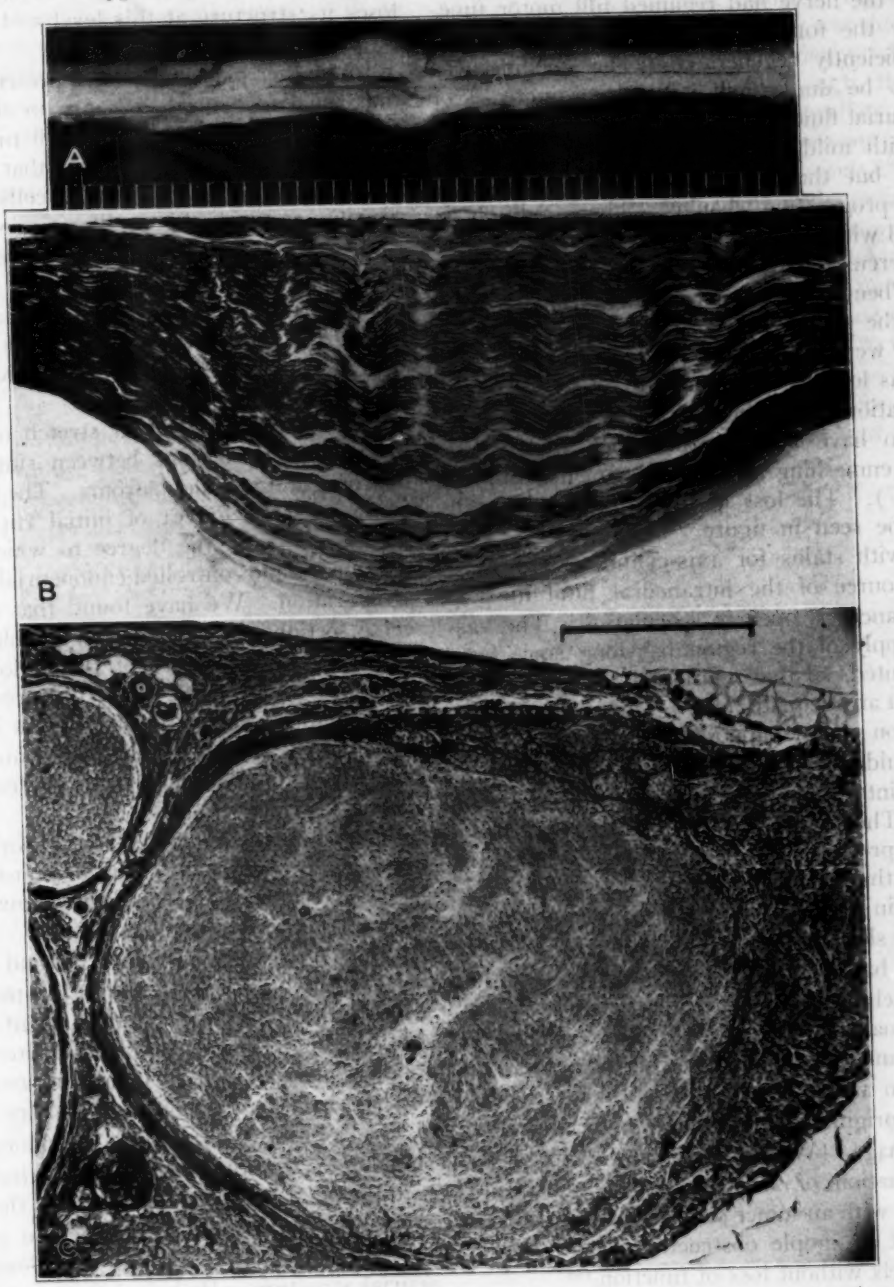

Fig. 7.—Sciatic nerve of cat, showing a pseudoneuroma which had persisted seven months after a percussion causing transient paralysis, of less than six weeks. *B*, longitudinal section of one of the nodules, showing myelin sheaths. The myelin sheaths are paler (regenerated) in the distal part of the swelling (right). Spielmeyer method. *C*, transverse section of one of the nodules, showing reconstitution of the perineurium. The ruled line in the upper corner corresponds to 0.5 mm. Hematoxylin and eosin stain.

efficient repair of the hernia through regrowth of the perineurium. A few superficial fibers became caught in the scar, but the bulk of the nerve retained normal structure. After approximately five months the swelling still remained, though the nerve had regained full motor function by the forty-eighth day and histologically was efficiently regenerated. The swelling was seen to be due chiefly to a local increase of endoneurial fluid. Some increase of endoneurial cells with mild deposition of collagen had occurred, but there was no indication that this was a progressive change. The condition is identical with that which we have found to result from percussion of nerve, and which might be called "benign pseudoneuroma." Since we reported the production of such swellings by percussion, we have seen examples of this swelling persist as long as seven months (fig. 7) without deterioration of function. The perineurium was found to have been reconstituted, though not without enmeshing some bundles of nerve fibers (fig. 7 *C*). The loss of fibers was very small, as can be seen in figure 7 *B* and as was confirmed with stains for axis-cylinders.

The source of the intraneural fluid in such circumstances is open to speculation. The vascular supply of the region has long since been reconstituted, so that continued venous congestion is not an adequate cause. There is no evident obstruction of any supposed circulation of intraneural fluid, for the tissue spaces merge imperceptibly into those proximal and distal to the injury. The obstruction is at the point of damage, not proximal or distal to it. We have to conclude that once highly albuminous fluid collects within endoneurial spaces its removal is an extremely slow process. The patches of "edema" which we have found in lesser degrees of injury from stretching, and then clearly related to damage to small blood vessels in the epineurium (fig. 2 *D* and *E*), are of identical nature, and for this reason we are inclined to believe that the fluid was originally a transudate associated with tissue damage. We have previously noted the early formation of such edema as a result of percussion with an intact perineurial sheath [3] and as a result of simple obstruction of the neural blood vessels without loss of function.[14a]

After a large herniation, both the hernia and the center of the neural fasciculus for a distance proximal and distal to it showed rapid dissolution of both myelin and axis-cylinders. This process was much more rapid than wallerian degeneration, and, in view of its occurrence under conditions of persistent severe but incomplete ischemia,[14a] we feel that it can be attributed to the accompanying dislocation and rupture of small blood vessels. More important in ultimate effect are a widespread proliferation of endoneurial fibroblasts within the swelling and their diffusion into neighboring tissues. The nerve loses its structure at this level and is converted into a solid neuroma.

In another place [15] we have presented evidence that the endoneurial cells are in the nature of fibroblasts, which respond to all manner of injury with multiplication, and that the natural function of the flat mesothelial cells of the perineurium restrains this proliferation. The present experiments indicate that the difference between the benign pseudoneuroma and the true spindle neuroma is related to the degree of disorganization of the architecture of the nerve bundle, and this, in turn, to the extent of fibroblastic proliferation.

It has been shown that stretch of nerve can produce all gradations between simple pseudoneuroma and spindle neuroma. The determining factor was the extent of initial rupture of the perineurium and the degree to which repair of that membrane controlled endoneurial fibroblastic proliferation. We have found that after transverse section of nerve the few fibroblasts in the perineurium join those of the endoneurium in the formation of scar tissue. The present experiments indicate that after small tears in the perineurium the flat mesothelial cells can repair the gap, although fibroblasts are also entangled in them.

We have already alluded to the work of Black, Burns and Zuckerman [4] in demonstrating the tissue tensions which arise with penetrating injuries from high velocity projectiles. From this, there is no doubt that powerful and extremely rapid stretching of nerves near the path of such a projectile must be a common event. We feel that the high frequency of intraneural fibrosis found to result from such injuries must be due to perineurial rupture of the type here described.

The nodule which forms a pseudoneuroma is similar in size and general shape to that of a true neuroma. It is of importance for the surgeon to be able to distinguish the benign edematous swelling from the fibrous scar with loss of endoneurial structure. Both feel firm and resistant. The true neuroma should be adherent to surrounding structure: the pseudoneuroma, of smooth and unbroken surface. Unfortunately, however, the initial injury, especially if due to a high velocity projectile, often results in extraneous scar tissue, which closely surrounds the nerve and obscures observation of its perineurium. A test of perineurial continuity would

therefore appear to be necessary. Injection of saline solution along the neural fasciculus appears rational, and the method has been frequently used. It is open to the objection that if too great force is used, rupture of the internal structure of the bundle and small vessels will be caused. Until some other method, such as the use of a vital dye to stain the scar, has been developed, injection of saline solution remains the only method generally applicable.

SUMMARY AND CONCLUSIONS

The effects of stretching a peripheral nerve beyond the limit of physiologic elasticity are related to the degree of extension thus produced. In milder degrees of stretch there occurred damage to epineurial vessels, with resultant patches of ischemic changes in nerve fibers. In more severe injuries the perineurium was ruptured and the nerve bundle herniated.

After the milder purely ischemic lesions there was efficient regeneration. Recovery following rupture of the perineurium varied in proportion to the extent of herniation of endoneurium immediately following injury.

After mild herniation of perineurial contents the perineurium was repaired. A pseudoneuroma formed and persisted for as long as five months without impairing almost complete regeneration of the nerve fibers. The swelling was due chiefly to the presence of fluid in the endoneurial spaces.

After severe herniation through the perineurium the nerve fibers in the swelling, and for a distance on either side, underwent necrosis. This damage was probably the result of the related vascular damage. The endoneurial fibroblastic tissue then proliferated in the manner of a neuroma, soon obliterating all trace of the original structure of the nerve at the level of the swelling, which thus became a true neuroma.

The ballistics involved in injuries to the limbs by high velocity projectiles are such as to induce stretch injuries to nerves at a distance from the track of the projectile and thus to lead to lesions in continuity.

Boston City Hospital (18).

THE CENTRAL NERVOUS SYSTEM IN UREMIA

A CLINICOPATHOLOGIC STUDY

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Uremia, because of its frequent renal origin, has been a subject of investigation primarily of the internist. For this reason, the greatest emphasis in the more recent literature has been placed on the renal and chemical aspects of this disease in spite of the fact that some of the most outstanding symptoms are neuropsychiatric in nature. The most common complaints referable to the nervous system are convulsions and coma. Addison,[1] as early as 1839, characterized the cerebral symptoms as "dullness of the intellect, sluggishness of manner, drowsiness going on to quiet stupor and ending in coma, often with convulsions." Although these are the better recognized forms of cerebral symptoms, a careful survey of a large series of cases will demonstrate almost every type of neuropsychiatric involvement, from the purely ascending motor disturbances to the full-blown psychoses of almost every type. The significance of the cerebral involvement which occurs in this illness was well recognized by the clinicians of a half-century ago, but this aspect of the problem has almost entirely disappeared from the recent literature. It was for the purpose of again emphasizing the clinicopathologic aspects of the effect of uremia on the central nervous system that the present study was undertaken.

It has long been recognized that uremia produces definite tissue changes within the central nervous system. The extreme importance of such changes was emphasized by the occasional occurrence of a striking chemical improvement in respect to nitrogenous metabolities of the blood, associated with a stubborn persistence of the various clinical symptoms, particularly those related to the nervous system. Because of the frequent predominance and severity of neuropsychiatric symptoms in this disease, many of the earlier investigators studied the brain in fatal cases to determine the nature of the occurring lesions. As a result of these investigations, descriptions of a wide variety of lesions accompanied with numerous individual interpretations have appeared in the older literature. The most prominent findings have been described as occurring within the cerebral cortex, although almost every part of the nervous system has been implicated. The chief histopathologic alterations associated with uremia seemed to involve the cortical neurons. Such changes have been reported by Bodechtel,[2] Hechst,[3] Rives,[4] Hiller and Michalovici,[5] Uchida,[6] Grinker,[7] Weiman,[8] Weil[9] and Mikuriya.[10] The cell changes were most variable in degree and in distribution. Most commonly, there occurred an irregular loss of tinctorial properties involving scattered elements of the various cortical areas, chiefly the third and fifth laminas. (Bodechtel,[2] Hechst,[3] Rives[4]). In some cases this tinctorial loss was severe, producing actual foci of devastation (Hechst[3]). In the cases of acute type the cortical neurons frequently revealed severe swelling with partial or complete chromatolysis (Hechst,[3] Hiller and Michalovici,[5]

From the Department of Neuropsychiatry, University of Minnesota Medical School (Dr. Baker).

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Uchida;[6] Grinker,[7] Weiman [8]). Occasionally the damage to the nerve cells was much more severe and consisted of vacuolation (Uchida,[6] Hechst [3]), pyknosis (Weiman,[8] Weil [9]) or even fatty degeneration (Weiman,[8] Weil,[9] Hechst [3]).

Although the neuronal changes appeared to be the most consistent alteration, numerous other changes were observed within the cortex. Hechst [3] reported scattered foci of softening, while both Hechst [3] and Bodechtel [2] observed scattered areas of bleeding. The various investigators differ in their observations regarding the glial elements within the cortex. In some cases there was a mild astrocytic increase, which was perivascular (Hechst [3]) or diffuse (Mikuriya [10]). Mikuriya also observed numerous glial nodules within the cortex in some of his cases. Hechst, on the other hand, described degeneration and necrosis of the glial elements around many of the cortical blood vessels.

Alterations have also been reported within the cerebral white matter, involving both the myelin and the glial elements. The demyelination was usually focal in nature (Hechst,[3] Weil [9]) and in many cases was strictly localized to the perivascular regions (Grinker,[7] Hiller and Michalovici [5]). The glial changes were most variable and were both degenerative and proliferative. Weil [9] and Weiman [8] observed widespread destruction of the perivascular glia, while Bodechtel [2] and Hiller and Michalovici [5] reported astrocytic proliferation. Bodechtel [2] stated the belief that the glia proliferated focally to form nodules in cases of true uremia, while in cases of pseudouremia this gliosis was of a more diffuse nature. Mikuriya [10] observed no differences in the nature of the astrocytic increase in the different types of uremia.

These tissue changes, although most commonly observed within the cerebral hemispheres, also appeared in other parts of the central nervous system. The brain stem was frequently involved, producing extensive alterations within the cranial nerve nuclei (Hechst,[3] Weil,[9] Mikuriya,[10] Silvan [11]). Silvan [11] found that most of the damage in his case was limited to the bulbar region and the reticular formation and that the changes were correlated accurately with the clinical findings. The neuronal damage was often selective, involving the nucleus of the vagus nerve while sparing other nuclei in the same region, such as the hypoglossal. Mikuriya and Hechst reported areas of softening within the pons. Weil, Hechst and Mikuriya observed striking alterations within the basal ganglia. Hechst observed neuronal damage and large areas of softening, while Mikuriya found vascular changes with hyperemia and numerous petechial hemorrhages. Pontile lesions were described by Mikuriya,[10] Hechst [3] and Weil,[9] while definite, and often extensive, cerebellar alterations were reported by Hechst,[3] Weiman [8] and Weisenburg.[12]

A great deal of emphasis has been placed by many of the earlier workers on the vascular alterations and the changes within the choroid plexus. The nature of the vascular changes has been most variable. Hechst,[3] Hiller and Michalovici [5] and Pollak and Rezek [13] described chiefly a vascular congestion with scattered perivascular and petechial hemorrhages. Changes within the vessel walls have been recorded by many investigators (Boedechtel,[2] Hechst,[3] Weil,[9] Pollak and Rezek [13]). These vascular changes were variable. In some cases there occurred merely a splitting of the elastica interna (Hechst [3] Pollak and Rezek [13]), while in other cases actual hyaline and calcium alterations were reported (Hechst,[3] Weil [9]). Often extensive vascular damage resulted, with actual necrosis of many of the elements of the wall (Pollak and Rezek,[13] Bodechtel [2]). Perivascular edema was reported by Hechst [3] and Pollak and Rezek.[13]

The role played by the choroid plexus in the production of uremic symptoms has been the subject of much speculation. Von Monakow [14] found that the cerebral symptoms of uremia appeared suddenly, even though the changes in the blood and the degree of uremia remained unaltered. Because of this, he concluded that the cerebral symptoms could not be caused entirely by the toxic products within the blood but, rather, were due to some factor which allowed the toxins to act on the brain. He felt that the choroid plexus was primarily engaged in holding back the toxins and when they finally became severely altered they allowed the toxins to pass through to the brain, resulting in the sudden onset of symptoms. Because of the possible role played by the choroid plexus in uremia, many extensive studies have been made to find alterations within these structures

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in this disease. Many changes have been reported. The epithelium of the choroid villi has been observed to be either desquamated or greatly swollen and vacuolated (von Monakow,[14] Tannenberg,[15] Saito[16]). Granules often were present within the cell cytoplasm, giving the latter a thickened appearance (Saito[16]). The connective tissue around the vessels appeared proliferated, resulting in papillary widening. In contrast to these changes, two investigators (Bodechtel[2] and Hechst[3]) found no alterations within the choroid plexus which could not be accounted for by the age of the patient.

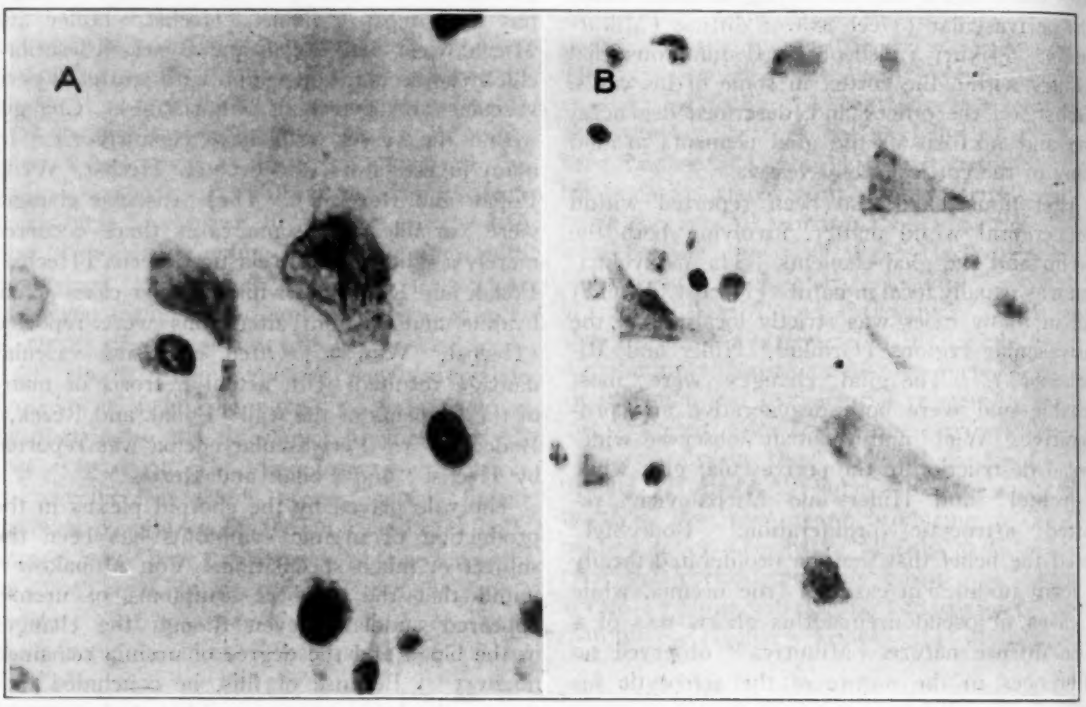

Fig. 1 (case 1).—Cerebral cortex. (*A*) The nerve cells are slightly swollen and show partial irregular chromatolysis. (*B*) Ghost cell formation. Two of the nerve cells have lost most of their tinctorial properties. A faint outline of some of the Nissl granules can still be seen within these cells. Nissl stain.

We have had the opportunity of studying in detail the tissues in 12 cases of fatal uremia and have selected 5 of these for presentation in the present report. In the latter group, the illness was fairly acute in 1 case and moderately or definitely prolonged in the others. Since the duration of the uremic process seemed to be the most important factor in determining the severity of the cerebral changes, we felt that such a selection of cases would offer a better opportunity to trace carefully the development of the pathologic alterations within the nervous system and to correlate such changes with the clinical symptoms. For the pathologic studies, blocks were taken from areas throughout the nervous system and were prepared for study by the following technics: hematoxylin and phloxine stain, Nissl's stain (thionin), the Weigert–Van Gieson stain for blood vessels, Bodian's stain for axons, Pal-Weigert's and Weil's stains for myelin sheaths and Cajal's gold chloride-mercury bichloride impregnation method for astrocytes.

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REPORT OF CASES

CASE 1.—A 5 month old child had acute extrarenal uremia. Autopsy revealed acute changes in the nerve cells involving chiefly the cortex and the brain stem. Early perivascular demyelination and mild perivascular bleeding were present within the cerebral white substance.

History.—S. A., a 5 month old girl, was brought to the hospital on Dec. 12, 1941 because of severe diarrhea, which had been present for one week. The baby was more irritable than usual on the morning of admission, at which time her temperature was 102 F. Vomiting was present.

On admission to the hospital the infant was in extremis. She was extremely cyanotic, and her respirations were shallow and infrequent. Her body was hot, but the extremities were cold. The temperature was 106 F. Her eyes were glassy and dull; the lips were

dry, and the neck was flaccid. The breath sounds were obliterated by mucus in the throat. The heart tones were inaudible. The blood urea nitrogen measured 71 mg. per hundred cubic centimeters, and the carbon dioxide-combining power was less than 3 volumes per cent. Oxygen was started immediately, and the baby rallied for a few moments, with slight decrease in the degree of cyanosis. An attempt was made to start intravenous injection of fluid, but less than an hour after admission the patient died.

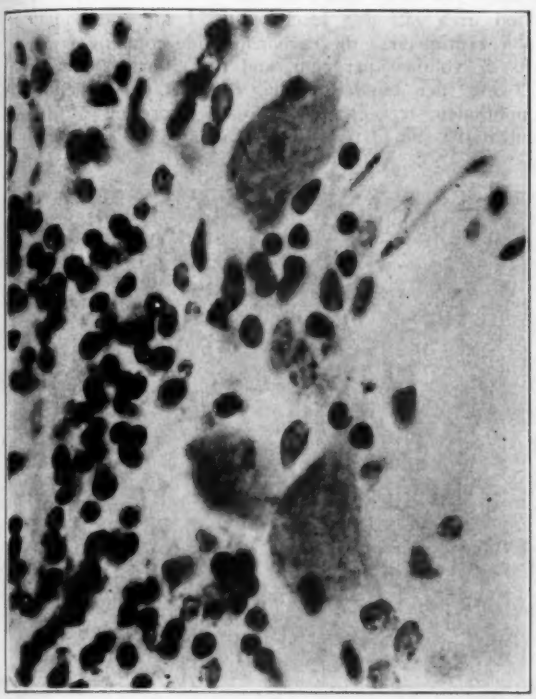

Fig. 2 (case 1).—Cerebellum. The Purkinje cells are greatly swollen. Most of their processes are absent, giving the cells a rounded appearance. Nissl stain.

Autopsy.—The body was that of a poorly nourished white female infant. The lungs showed a few areas of atelectasis, and the posterior portions were congested. There were four areas of intussuception in the small intestine, which probably represented agonal change. The other organs were normal. Gross examination of the brain revealed a relatively mild brownish pigmentation disseminated over the surface of the brain. The cerebral cortex was congested and contained scattered perivascular extravasations.

Microscopic Examination of Brain.—The gray matter of the hemispheres revealed scattered changes within the nerve cells, consisting primarily of mild swelling and partial or complete chromatolysis (fig. 1 *A*). Some of the cells had completely lost their ability to stain and appeared as ghost cells (fig. 1·*B*). The cell processes often were detached, producing a swollen, rounded appearance. The nuclei, as a rule, were uninvolved. These neuronal changes showed a distinct tendency to be patchy, with the involved elements surrounded by large groups of structurally intact cells. On cursory examination the subcortical tissues appeared unchanged. However, the special stains revealed early focal changes in the myelin, consisting chiefly of slight swelling of the sheaths. The axons within these areas showed no structural changes.

The nerve cells within the basal ganglia revealed moderate diffuse chromatolysis but no nuclear changes. The smaller arteries were congested and occasionally surrounded by distended perivascular spaces containing erythrocytes.

The cerebellum was extensively involved. Many of the Purkinje cells had lost most of their tinctorial properties and were difficult to outline adequately. The cells that did accept the stain appeared swollen, and their processes were fragmented or even absent (fig. 2).

Acute changes in the nerve cells were present within scattered regions of the brain stem, implicating chiefly the descending roots of the trigeminal nerves, the hypoglossal and the medial vestibular nuclei and the nuclei solitarii. The involved neurons showed chiefly pronounced swelling and chromatolysis but no nuclear alterations.

Case 2.—A man aged 36 entered the hospital with complaints of visual disturbance, nausea and vomiting. The blood urea nitrogen measured 220 mg. per hundred cubic centimeters. He died within twenty-four hours, during a convulsive seizure. Autopsy revealed acute and chronic changes in the nerve cells, involving chiefly the cerebral cortex and the brain stem. There were scattered areas of perivascular and focal demyelination in various stages of alteration and repair.

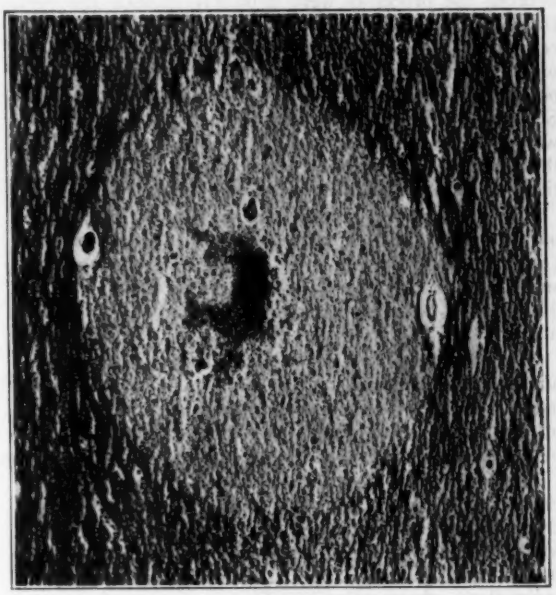

Fig. 3 (case 2).—Perivascular demyelination within the white matter. The involvement is almost complete and is sharply circumscribed. Pal-Weigert stain.

History.—E. G., a 36 year old farmer, entered the hospital on Nov. 2, 1943. Ten months previously he was first told that he had high blood pressure. In July he noticed some difficulty with vision. Two weeks prior to admission, nausea developed, and he had occasional periods of vomiting. Spontaneous epistaxis began the morning of admission.

Examination revealed that the patient was dyspneic, slightly lethargic and uncooperative. A systolic murmur was heard at the apex, and the aortic second sound was accentuated. Pitting edema was present over both ankles. The urine had a specific gravity of 1.010 and

contained albumin, some red blood cells and many white blood cells. The blood urea nitrogen measured 220 mg.; the cholesterol, 246 mg.; the calcium, 11 mg., and the phosphorus, 14.8 mg., per hundred cubic centimeters.

The patient failed rapidly in spite of oxygen, diuretics and attempted rapid digitalization. He died twenty-four hours after admission, after a generalized clonic convulsion.

Autopsy.—About 30 cc. of fluid was present in the pleural cavities. The lungs were edematous and congested. The kidneys were small; the right weighed 130 and the left 115 Gm. There was fine pitting of their external surfaces, and on section the cortices were narrowed and yellowish. Gross examination of the brain showed some fibrosis of the meninges in the region of the hypothalamus. Coronal sections revealed sparsely disseminated petechiae throughout the cerebrum, especially in the white substance.

Microscopic Examination of Brain.—The cerebral cortex showed numerous changes, involving both the cellular and the interstitial elements. The cortical neurons were irregularly but diffusely involved throughout both cerebral hemispheres. The most frequent alteration consisted of diffuse chromatolysis, often associated with nuclear changes. The cell nuclei were often situated eccentrically and revealed definite changes in shape, size and membrane structure. In a few neurons the processes were definitely swollen and even fragmented. Aside from these changes in the nerve cells, there were many striking tissue alterations. Many of the cortical vessels were surrounded by distended perivascular spaces or areas of definite demyelination. Scattered areas of softening apparently unassociated with the vessels were also observed. In some cases these softened areas had resulted in tiny cavity formations already surrounded by a mild glial scar.

The white matter exhibited scattered areas of demyelination, most of which were perivascular in distribution (fig 3). In addition, there were observed numerous small foci of necrosis filled with fat granule cells. A diffuse glial increase was noted throughout the white matter.

The thalamus revealed chronic changes. There was an apparent decrease in the number of neuronal elements. Many cells were shrunken and pyknotic. Areas of old tissue injury with resultant vacuolation were observed near the walls of the third ventricle.

The brain stem also revealed neuronal and interstitial changes. Many of the cells of the facial nuclei were chromatolytic and vacuolated and even showed a nuclear loss. The cells of the mesencephalic root of the trigeminal nerve showed acute swelling associated with perinuclear chromatolysis. This entire nucleus was almost completely destroyed, hardly a normal cell remaining. Similar swelling and chromatolysis appeared in many of the neurons within the pontile nuclei. Focal areas of demyelination occurred in the region of the trapezoid body. Numerous glial nodules were scattered throughout the brain stem. The vessels were structurally uninvolved.

CASE 3.—A 26 year old housewife, with a history of renal trouble since infancy, had had diarrhea and vomiting for one month. The blood urea nitrogen level was 254 mg. per hundred cubic centimeters on her admission and dropped to 50 mg. per hundred cubic centimeters with treatment. Convulsions appeared in spite of improvement in laboratory findings. Autopsy revealed widespread devastation of the neurons and extensive myelin changes, involving all areas of the brain.

History.—R. B., a 26 year old housewife, entered the hospital on Dec. 14, 1943, with a history of diarrhea and vomiting of one month's duration. She had had nocturia during this time but no dysuria, hematuria or pyuria. She had had renal trouble since the age of 2 years, the disorder following scarlatina.

Examination revealed that the patient was well nourished and well oriented. Her mouth contained ulcerated areas over both buccal regions and under the tongue. There was slight pitting edema over both tibias. The urine had a specific gravity of 1.010. The blood urea nitrogen level was 254 mg. per hundred cubic centimeters; the carbon dioxide–combining power was 27 volumes per cent, and the chlorides measured 572 mg. per hundred cubic centimeters. Phenolsulfonphthalein tests showed a total excretion of 3 per cent at the end of two hours.

Fig. 4 (case 3).—Focal and perivascular areas of demyelination. The changes are very early and are fairly well localized. Weil stain.

Although the patient's acidosis was readily corrected by administration of saline solution and the high level of urea nitrogen was reduced to 50 mg. per hundred cubic centimeters, the patient failed to improve clinically. In spite of an almost normal urea nitrogen level, about one week after admission she suddenly had her first convulsion. The convulsions were chiefly of a grand mal type and were preceded by a cry and followed by long periods of unconsciousness. In the intervals between the attacks, her muscles would twitch and her arms would jerk in an irregular manner. The convulsions increased in frequency, and the patient gradually became confused and disoriented and died Jan. 7, 1944.

The creatinine level of the blood was 6.9 mg. per hundred cubic centimeters on December 20, and two days later it had risen to 190 mg. The neurologic examination on December 25 revealed the pupils to be dilated but reactive to light and in accommodation. A

vertical nystagmus was present. The fundi were normal. The deep reflexes were normal. A Babinski sign was present on the right.

Autopsy.—There was edema of the face, eyelids and ankles. A few petechial hemorrhages were present over the abdomen. Gross examination of the brain revealed definite vascular congestion. This was most marked in the parieto-occipital region.

Microscopic Examination of Brain.—There was widespread devastation of the neurons in scattered areas throughout the cortex. Many of the cells were only mildly involved, showing only swelling and chromatolysis. Others were more severely damaged, resulting in marked tinctorial loss, vacuolation and even pyknosis.

Within the mesencephalon, the neurons of the oculomotor nucleus were widely involved. Scattered areas of perivascular demyelination were present within the substantia nigra. The nuclei of the vagus nerves were also diffusely involved, with most of the cells revealing either diffuse chromatolysis or early pyknosis. The ganglion cells of the spinal vestibular nuclei were pyknotic.

CASE 4.—Recurrent attacks of motor weakness occurred over a period of one year. The final attack appeared as an ascending paralysis, terminating fatally with bulbar palsy. The blood urea nitrogen measured 210 mg. per hundred cubic centimeters. Autopsy revealed both acute and chronic neuronal changes within

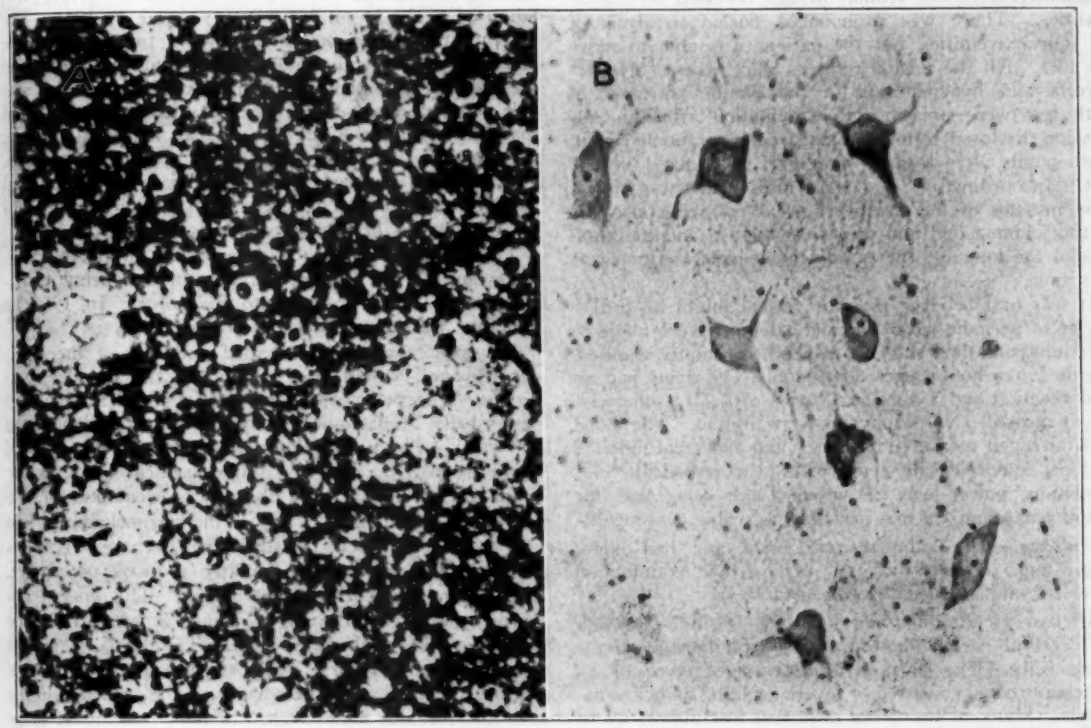

Fig. 5 (case 4).—*A*, small focal areas of demyelination. The adjacent myelin sheaths are moderately enlarged. Weil stain. *B*, anterior horn of the spinal cord. The cells show some swelling and extensive chromatolysis. Many of the cell processes have disappeared. Nissl stain.

Isolated areas of softening, filled with scavenger cells, were observed.

The white matter exhibited conspicuous focal and perivascular demyelination (fig. 4). In scattered lesions early cavitation appeared, surrounded by an irregular glial wall. These lesions obviously indicated a more chronic process. Small ball hemorrhages were noted. The walls of many of the smaller vessels when stained with special methods appeared frayed and often stained irregularly. Occasionally small ball hemorrhages were observed in the vicinity of such altered vessels. The globus pallidus exhibited widespread neuronal changes, consisting chiefly of chromatolysis. Early focal myelin damage was also visible. A diffuse glial increase was present.

Many of the Purkinje cells of the cerebellum had disappeared. Many of the remaining cells were altered, revealing diffuse chromatolysis or complete loss of their staining properties. The larger blood vessels of the cerebellum presented some thickening of the media.

the cortex and the nuclei of the brain stem. Numerous areas of perivascular and focal demyelination were observed within the white matter.

History.—A. H., a 45 year old farmer, was admitted to the hospital April 11, 1944, after having accompanied his daughter to the clinic, where she was undergoing investigation for pituitary basophilism. Apparently, he had been well until that forenoon, when there suddenly developed vomiting and a staggering gait. At this time he noticed weakness in his legs. This paresis ascended to involve the proximal muscles of his shoulders. His limbs rapidly became weaker, so that, when attempting to sign his daughter's admission papers, he slumped to the floor and had to be admitted to the hospital.

Information from his wife revealed that he had not been well since November 1943, when he had severe diarrhea associated with anorexia and loss of weight. One year previously he had a similar episode of weakness of the limbs, which subsided after a short nap.

In January 1944 he suffered what was termed a "stroke." His whole right lower extremity suddenly became painlessly paralyzed. He gradually recovered after a three week rest in bed. He had had nocturia, with micturition four to five times a night, all his life. Increased frequency was also present during the day. At about the age of 12 years he had had a kidney "drained," as it was supposed to have been enlarged and infected. His mother and a sister died of diabetes.

Examination of the patient shortly before admission to the hospital revealed that he was fully oriented. The exposed surfaces of the skin were deeply tanned. The heart tones were muffled. The blood pressure was 116 systolic and 80 diastolic. He was unable to sit up or hold his head erect. The fundi were normal. Examination of the cranial nerves revealed no abnormalities. There was pronounced flaccid paralysis of all four extremities, but the patient was able to move his toes. All the tendon reflexes were absent. Hyperalgesia and hyperesthesia of the plantar surfaces of both feet were present. Reexamination after his admission disclosed signs of extensive bulbar involvement. Both pupils were slightly irregular, particularly on the left. Incoordination of ocular movements was noted. The muscles of the jaw were weak, as were also the sternocleidomastoid and trapezius muscles and the muscles of the tongue. Increased tendon pain was noted at this time.

It was first believed that the patient might be suffering from periodic paralysis, and attempts were made to give him potassium chloride, which he promptly vomited. He died five hours after admission. The urine had an acid reaction and a specific gravity of 1.021; otherwise it was normal. No porphyrins were present. The blood urea nitrogen measured 210 mg., and the creatinine, 12 mg., per hundred cubic centimeters; the carbon dioxide–combining power was 25 volumes per cent; and the serum potassium, 32 mg. per hundred cubic centimeters.

Autopsy.—The kidneys were small and had blebs, 2 to 3 mm., on their surfaces. Microscopic examination revealed far advanced pyelonephritis.

Microscopic Examination of Brain.—Sections through the cerebral cortex showed widespread damage to the nerve cells. The most striking changes were of an acute nature and consisted of severe swelling and chromatolysis. Many of the nerve cells had lost almost all of their staining properties and remained as ghost cells. Interspersed among these acutely involved elements were scattered cells showing pyknosis and shrinkage and representing the remains of a more chronic and long-standing process. There was a diffuse glial increase, particularly about the vessels.

The white matter exhibited an extensive but patchy demyelination, which was most prominent about the smaller vessels, including capillaries (fig. 5*A*). In some regions this focal demyelination had resulted in the formation of small cavities, many of which were surrounded by a glial wall, of varying thickness. Glial nodules could be detected throughout the white matter.

Sections through the brain stem disclosed extensive changes within many of the cranial nerve nuclei. There was softening with complete destruction of the underlying tissue of the nuclei of the vagus nerves. The cells were swollen, fragmented and chromatolytic. Their nuclei were swollen and vacuolated. The nerve cells of the nucleus ambiguus and the descending root of the trigeminal nerve on both sides revealed primarily swelling and chromatolysis of scattered elements. The peripheral nerves appeared normal.

The spinal cord exhibited both acute and chronic changes. The anterior horn cells were swollen and rounded, having lost their processes (fig. 5 *B*). There was no vacuolation or fragmentation. The residual of chronic involvement was seen in a few small scattered, shrunken cells, the processes of which had disappeared, leaving only a small, round, distorted mass as the remnant of the injured nerve cell.

CASE 5.—A 31 year old man, with extrophy of the bladder, gave a history of recurrent attacks of motor weakness over a period of eight years. On his last admission he presented quadriparesis. The blood urea nitrogen measured 74.1 mg., and the serum potassium, 8.9 mg., per hundred cubic centimeters. He died within twenty-four hours after his last admission, of respiratory failure. Permission for autopsy was refused.

History.—A. L., a 31 year old truck driver, was admitted to the hospital dispensary April 18, 1944. The patient stated that one month prior to admission he had awakened in the morning to find his arms and legs paralyzed. About an hour later, however, he was able to dress and see his local physician, who thought that this disturbance might be due to his renal trouble. He had had two subsequent attacks of motor weakness. The last one occurred two weeks before admission and persisted for three days. He had had no convulsions or difficulty in breathing or swallowing.

The patient was born with extrophy of the bladder, for which he had four operations, the last being transplantation of the ureters into the colon. In 1936 he had four transient attacks of motor paralysis.

Physical examination revealed extrophy of the bladder, through which the mucosa of the bladder was visible. The penis was retracted, and the testes were descended. Neurologic examination revealed nothing abnormal. Three days later the patient was admitted to the hospital because of a sudden return of neurologic symptoms. At this time there was weakness of the left medial rectus muscle and of the sternocleidomastoid and trapezius muscles bilaterally. The deep reflexes in the upper limbs were greatly reduced or absent. The abdominal reflexes were absent. The knee jerks were hyperactive, the right being greater than the left; the ankle jerks were absent. Gordon's sign was positive on the right. The patient was able to flex slightly the fingers of both hands. The muscles of the arm and forearm were weak. In the lower limbs there appeared to be weakness only of the gastrocnemius and soleus muscles; the peroneal group was normal. Sensation was intact. Urinalysis could not be carried out because the urine was passed by rectum. The blood urea nitrogen measured 49 mg., and the creatinine, 2.1 mg., per hundred cubic centimeters, and the carbon dioxide–combining power 38 volumes per cent. The serum potassium level was 17.3 mg. per hundred cubic centimeters. A phenolsulfonphthalein test, carried out by means of enemas, yielded an excretion of 20 per cent at the end of forty-five-minutes. Roentgenographic studies of the kidneys revealed rather marked hydronephrosis of both calices and pelves. The ureters were moderately dilated. A lumbar puncture revealed nothing abnormal. The patient's condition improved while he was in the hospital, and he was discharged when the acidosis was corrected, with instructions to return at the onset of his next attack.

The patient was readmitted on July 16, 1944. Two days prior to admission he noted weakness of his left thigh. This disappeared, but the next day his right thigh was weak. On the morning of readmission he awakened almost completely paralyzed. Examination now disclosed a slight horizontal nystagmus. Conver-

gence was poor. There was weakness of the trapezius muscle bilaterally, but more pronounced on the right. The deep reflexes in the right upper limb were reduced or absent, while those in the left were uninvolved. All the abdominal reflexes were absent. The right knee jerk was increased; the left was normal. Both ankle jerks were absent. There were no pathologic toe signs. Sensation was normal. There was generalized quadriparesis, more marked on the right. The weakness of the lower extremities was more pronounced distally than proximally.

Laboratory studies revealed the blood urea nitrogen level to be 74 mg. per hundred cubic centimeters; the carbon dioxide–combining power, 16.5 volumes per cent, and the serum potassium level, 8.9 mg. per hundred cubic centimeters. When the report on the serum potassium was obtained, the patient was given 1.5 Gm. of potassium chloride intravenously. The serum potassium level one-half hour later was only 6.1 mg. per hundred cubic centimeters. The patient showed no improvement. Cardiac arrhythmia and respiratory distress developed, and he failed to recover with use of the Drinker respirator and cardiac stimuli. Administration of more potassium chloride was not beneficial, and the patient died shortly thereafter. Unfortunately, permission for autopsy was not granted.

CLINICAL FEATURES

The symptoms of uremia can be divided roughly into two groups: those of depression of the central nervous system, e. g., apathy, muscular weakness, stupor and coma; and those of neuromuscular hyperexcitability, namely, increased tendon jerks, muscular twitchings and convulsions. The former are by far the more common and appear earlier in the illness. The patient may appear mentally and physically fatigued, tiring easily and being unable to concentrate. Dull, constant, but not severe, headaches often develop. The patient soon becomes apathetic and complains of muscular weakness and a constant feeling of drowsiness, while at the same time he may have periods of restlessness and intractable insomnia. Clouding of the sensorium, although occurring, is not the rule, many of the patients remaining well oriented until death. Speech, however, may be difficult and often unintelligible.

Symptoms of neuromuscular hyperexcitability, namely, muscular twitchings and convulsions, are frequent with uremia and often accompany the picture of lethargy, stupor or coma. The muscular twitchings are usually fibrillary and may involve large muscle groups (Oppenheimer and Fishberg [17]). The convulsions usually appear terminally and are generalized. Focal or jacksonian seizures may occur but are uncommon. Occasionally these epileptiform seizures continue even after the patient has recovered from the uremia, indicating the persistence of cortical irritation or cerebral damage.

Aside from these better known neurologic symptoms, there occur with uremia a host of less common, and often bizarre, signs, which frequently cover the entire field of neuropsychiatric symptomatology. It is when these predominate that the diagnosis is often overlooked. Most frequent are the vague, and often unusual, neurologic syndromes. Monoplegias hemiplegias, aphasias and apraxias have been reported (Fishberg,[18] Osler,[19] Saito,[16] von Monakow,[20] Boinet [21]). Of the motor symptoms, hemiplegia is the most frequent. This usually is of a flaccid type and is often ascending, producing Landry's type of paralysis. The involvement is transient, lasting hours or days and then disappearing, only to return after a variable period. Two of our patients had such episodes; in 1 the involvement implicated all limbs, resulting in quadriplegia. Hiller and Michalovici [5] described a case in which right hemiplegia with palsy of the left side of the face developed in a 26 year old man. Rothmann [22] described a case of transient amaurosis. This amaurosis may be associated with convulsions and may even remain as a permanent defect (Osler [19]). Uremic deafness can occur. Vertigo and nystagmus are infrequent symptoms (Bodansky and Bodansky [23]).

In an occasional case of uremia the mental symptoms may be the earliest, and often the predominating ones throughout the illness. The most frequent picture consists of acute confusion associated with motor unrest, incoherence and terrifying hallucinations. Occasionally there is a rapid change in mood from uncontrollable hyperactivity to depression, accompanied with hypochondriasis and delusions of persecution. Almost every form of mental illness has been described in cases of uremia, from profound melancholia to typical catalepsy with echolalia, negativism and waxy flexibility (Lemierre,[24] von

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Hauth,[25] Menninger,[26] Bischoff,[27] Marcus,[28] Kleudgen,[29] Jacobson,[30] Grimshaw,[31] Cullerre,[32] Hagen,[33] Hoesslin[34]). Mental deterioration may occur and can be transient or permanent, depending on the severity of the cerebral injury.

Since the cerebral symptoms are not specific but merely indicate some type of involvement of the nervous system, one must always seek for any additional symptoms or signs that might help in the diagnosis. These are frequently found in the accompanying gastrointestinal symptoms and the alterations in the blood chemistry. The gastrointestinal symptoms usually consist of uremic stomatitis, a uriniferous odor of the breath, vomiting and diarrhea. The changes in the blood chemistry associated with uremia are well known and need no discussion.

PATHOLOGIC FEATURES

A detailed histopathologic study of the central nervous system in fatal cases of uremia clearly indicates that if the illness is sufficiently prolonged, structural damage will result. The nature of these tissue changes varies primarily with the duration of the disease.

Acute Illness.—Gross Changes: The central nervous system may be entirely normal or may exhibit mild changes, varying from congestion to definite petechiae. Cut sections may reveal scattered punctate hemorrhages, which usually remain discrete.

Microscopic Changes: The predominant alteration in cases of acute uremia occurs within the neurons throughout the central nervous system. The earliest changes consist of pronounced swelling and partial, or even complete, chromatolysis (fig. 1 *A*). Very early these swollen cells tend to lose their staining properties, forming ghost cells (fig. 1 *B*). The cell processes often become detached, giving the cells a swollen, rounded appearance. The cell nucleus seems to be the least affected, and even in apparently severely injured elements they remain structurally uninvolved. At times the nucleus may appear mildly swollen and eccentrically placed. These neuronal changes are widely scattered and show no tendency to localize within any region. Usually the injured cells are observed scattered among apparently normal elements. In the cases of more severe and prolonged uremia, large areas of cellular devastation can be made out. Within the cerebellum, the Purkinje elements are most frequently implicated, many of them showing fragmentation of their processes, as well as an irregular loss of staining properties (fig. 2). Here, too, the nuclei appear intact. In all cases the cranial nerve nuclei are definitely involved. No particular structures appear to be selected by this process, different nuclei being involved in different cases. The cell changes are all of the acute type, producing swelling and chromatolysis.

Throughout both the gray and the white matter there appears marked vascular congestion, with some perivascular extravasation. Scattered petechiae may occasionally occur.

In those cases in which the illness lasts over five days a very early perivascular and focal demyelination results. These changes are more prominent within the white matter but do occur within the cortex and the brain stem. The perivascular myelin sheaths become swollen and occasionally fuse to produce tiny vacuolated spaces. No cellular reaction can be seen within these areas of acute perivascular alterations. Glial changes are usually not seen.

Subacute Illness.—When the illness lasts from a few weeks to a few months, the tissue changes are much more severe and more widespread. The neuronal involvement is prominent, particularly in the cerebral cortex and in the brain stem, where large areas of adjacent cells are injured, often producing actual areas of devastation. The nature of the injury to the nerve cells is much more variable than with the acute illness. Many of the cells still show the typical acute changes, with severe swelling and chromatolysis; however, others reveal more chronic alterations, with definite nuclear damage. Even within the acutely altered cells the pathologic process seems to be more severe, and the cell body reveals actual fragmentation, with only small fragments of cytoplasm adhering to an intact or greatly altered nucleus. Ghost cells

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are numerous. Scattered among these swollen and fragmented elements are many nerve cells that have undergone a chronic change (fig. 6). Both the cell body and the nucleus appear pyknotic; the Nissl granules are coarse and clumped, and the cell processes are retracted, narrowed and blunt. This admixture of acute and chronic damage to nerve cells is prominent within the cranial nerve nuclei, where occasionally all the components of a nuclear group show some involvement, without leaving a single structurally intact cell.

The demyelination in this stage of the disease is also much more extensive and, although

Fig. 6 (case 3).—Subacute neuronal changes within the cortex. The cell body has undergone some fragmentation, leaving only cytoplasmic fragments adhering to the nucleus. Nissl stain.

appearing within the cortex, is much more prominent within the white matter. This demyelination is both focal and perivascular and extends for considerable distances into the adjacent tissues (figs. 4 and 5 *A*). In many of these perivascular areas the demyelination is almost complete and is partially replaced by fat granule cells (fig. 3). In addition to this demyelination, there occur scattered foci of necrosis, often filled with necrotic brain tissue and fat granule cells. In an occasional field these necrotic areas have been fairly well cleared of injured brain tissue, producing tiny cavity formations. The glia shows a mild diffuse increase. The greatest tendency for glial reaction appears to be in the vicinity of the necrotic foci. Vascular congestion is not conspicuous in this stage of the illness, although scattered ball hemorrhages are frequently encountered.

Chronic Illness.—When the illness lasts many months or years, the predominant tissue change tends to be parenchymal rather than neuronal. The nerve cells now reveal predominantly chronic alterations, consisting of pyknosis and shrinkage. Many of the cells appear as tiny dark masses, within which none of the cell structures can be identified. Many neurons have entirely disappeared, leaving a considerable reduction of the normal elements. This complete disappearance of cells is most noticeable in the cerebellum and the brain stem. Frequently acute changes accompany the more chronic ones, indicating continuation of the pathologic process.

The demyelination and tissue necrosis are striking in this stage of the illness. Both are associated with fat granule cell reaction. In many areas these foci of tissue injury have resulted in the formation of small cavities, many of which contain a few scavenger cells and are surrounded by a glial wall, of varying thickness. Glial nodules occasionally are present throughout the white matter.

Vascular congestion and petechiae are usually absent. The small vessels, in spite of the use of special staining technics, reveal no consistent changes within their walls. In a few scattered vessels the walls reveal patchy impairment of their staining properties.

COMMENT

The question might be raised as to whether the lesions described were due entirely to the uremic intoxication, since many patients with uremia do have a pathologic condition of the kidneys associated with circulatory abnormalities. In order to reduce to a minimum such complicating vascular alterations or changes due to age, an attempt was made to select for study primarily cases from the younger age group, in which the vascular abnormalities would be less likely to occur. Moreover, 4 of our patients suffered from extrarenal uremia, with no indication of a pathologic condition of the kidneys. In none of the reported cases was there any significant pathologic evidence of circulatory disturbance. This absence of detectable cerebrovascular lesion, the constancy of the histologic changes and their increased severity with the more chronic disease and, finally, the simi-

larity of the observations in both the renal and the extrarenal forms of uremia forced us to conclude that these changes were probably produced by the uremic intoxication.

The possible cause of such cerebral complications in cases of uremia still remains a moot question in spite of extensive investigations. The experimental data thus far accumulated would indicate that the uremia syndrome is the result of a disturbance of electrolytes, an increase in nitrogenous metabolites within the blood or the evolution of some toxin hitherto unrecognized. The last view finds some support from the interesting investigations of Foster.[35] Basing his work on Herter's observation that the blood of uremic patients was more toxic to dogs than the blood of normal persons, Foster isolated a crystalline substance from uremic blood which killed guinea pigs when injected intraperitoneally. Some animals died of convulsions in fifteen minutes; others died less rapidly and prior to death had paresis or paralysis of the hindlegs. Foster's work, although extremely significant, has, unfortunately, not as yet been corroborated.

The work of Harrison and Mason[36] and Mason and associates[37] would indicate that in uremia the brain is subjected to two antagonistic influences, one stimulating, the other depressing. According to these investigators, the increased neuromuscular irritability is apparently due to more than a deficit of ionized calcium, as injections of a suitable calcium salt will not always alleviate the symptoms. De Wesselow[38] and Harrison and Mason[36] found no connection between the diminution of serum calcium and the generalized convulsions. Becher[39] and de Wesselow[38] placed a greater prognostic value on the rise in serum phosphates than on the deficit of calcium.

The depression in functions of the nervous system associated with uremia has been suspected by some to be due to a rise in blood phenols (Dickes,[40] Becher[39b] and Mason and associates[37]). These authors did not agree as to whether the phenols must be free or can be combined. Certainly, chronic phenol poisoning produces a clinical picture resembling that in some cases of uremia.

More recently, a great deal of interest has been centered on the significance of altered potassium levels of the blood of uremic patients. The recent work of Brown, Currens and Marchand[41] seems to indicate that too high a level of blood potassium is as dangerous as too low a level. Cardiac arrest may develop from either, as cases 5 and 6 in our series indicate. The changes in the electrocardiogram may be helpful in cases of this type.

SUMMARY AND CONCLUSIONS

1. Uremia, although usually treated by the internist, occasionally results in symptoms that may cover the entire field of neuropsychiatric symptomatology.

2. The most common symptoms referable to the nervous system are convulsions and coma, but in isolated cases unusual syndromes, such as monoplegias, hemiplegias, aphasias and apraxias, or even mental symptoms of almost every type, may be present.

3. The central nervous system in cases of uremia reveals widespread tissue changes involving both the nerve cells and the parenchymal elements. In the acute illness the predominant alteration occurs within the cortical neurons, which reveal an acute change in the nerve cells. In the more chronic illness the most striking changes are parenchymal rather than neuronal and consist of focal and perivascular areas of demyelination and necrosis. The neurons show both acute and chronic changes in the more chronic illness.

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ELECTROENCEPHALOGRAM OF DOGS WITH EXPERIMENTAL SPACE-OCCUPYING INTRACRANIAL LESIONS

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The controlled reproduction in laboratory animals of pathologic conditions which produce alteration in the electroencephalogram is one approach toward an understanding of abnormal brain waves. Foerster and Altenburger [1] have shown that tumor tissue itself is apparently electrically inert and that the changes observed electroencephalographically with such lesions are recorded from tissue surrounding the tumor. Hence it has seemed logical to use a noncellular material to simulate the space-occupying lesions observed clinically. The procedure of introducing foreign bodies in the brain is not new,[2] and the histologic changes from foreign bodies in the brain have been reported by several workers.[3] Experimental subdural and extradural hematomas in rabbits have been reported by Glaser and Sjaardema [4] to cause alteration in the electroencephalogram characterized by the disappearance of normal frequencies and the appearance of slow waves mixed with rapid activity.

An understanding of the alterations in the anatomic and physiologic state essential for the production of abnormal slow waves is one of the problems suggested by clinical electroencephalography. The term "delta wave" was coined by Walter [5] to describe such abnormally slow potentials seen in the electroencephalogram in cases of focal intracranial lesions. Pressure on cortical layers,[6] lowered excitability of cortical neurons from intoxication or circulatory embarrassment [7] and disturbance of pathways in the white matter [8] have each been advanced as a possible causative mechanism for these potentials.

METHOD

Records were taken with a Grass four channel, ink-writing electroencephalograph on 25 adult dogs that were trained to lie quietly in an animal holder, the muzzle of which prevented movements of the head. By use of steel needle electrodes [9] placed into the skull through the procainized scalp, it was possible to obtain records free from artefact. With anesthesia induced with pentobarbital sodium, a hollow threaded, stainless steel plug with a self-sealing rubber diaphragm (fig. 1 *A*) was screwed into a tapped hole through the parietal area of the skull of each dog without injury to the dura. Two weeks after operation, when the scalp had completely healed over the plug, electroencephalograms were taken and were compared with control records taken before operation to insure that there had been no damage to the underlying brain. A sterile mixture of white wax U. S. P. softened with iodochlorol (a radiopaque, chloriodized peanut oil) or liquid petrolatum was injected into the brain through a 20 gage hypodermic needle thrust through the surgically prepared, anesthetized scalp and the rubber diaphragm of the hollow metal plug (fig. 1 *B*). The injection was accomplished by means of a metal syringe, whose plunger was activated in "grease gun" fashion by a threaded turnscrew. After the injection, electroencephalograms were taken at frequent intervals, until the experiment was terminated with a bilateral craniotomy performed with the dog

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Dr. Robert Dow directed this study, and Dr. Knox Finley gave guidance in neuropathologic interpretation.

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under ether anesthesia. At this time 1 mm., cotton wick core, steel tube electrodes were placed, four on each side of the exposed cortex. After liberal use of procaine hydrochloride in the scalp, the ether anesthesia was stopped, and electrocorticograms were taken over periods of up to three hours. The animal was then killed with an overdose of pentobarbital and the brain removed, fixed in 95 per cent alcohol or in solution of formaldehyde U. S. P. diluted 1: 10, embedded in pyroxylin or paraffin, cut at 20 microns and the sections stained with hematoxylin and eosin and with the methods of Nissl and Weigert.

RESULTS

Brain Potentials of the Unanesthetized Dog.—The electroencephalograms recorded from 40 normal unanesthetized dogs in this laboratory have been characterized by a dominant frequency of from 20 to 30 cycles per second. Occasional waves at lower frequencies were seen, especially in younger dogs. Electrocorticograms were obtained from the exposed brain in 16 dogs with the scalp under local anesthesia. The electrocorticograms resembled the electroencephalograms in all ways except for an increased voltage. In animal recordings one must be constantly on guard for artefacts due to muscle potentials and to respiratory and other movements of the animal. Liberal use of procaine in the scalp, training and close observation of the animal and rigid fixation of the head resulted in records which were relatively free from artefacts.

Dogs with Intracerebral Lesions.—Successful intracerebral injections of white-wax mixture were accomplished in 20 dogs, and electroencephalographic tracings were taken from one minute to four months after the injection. Except in 3 dogs in which there occurred a slight diminution of amplitude of the spontaneous activity on the side of operation the surgical placement of the metal injector caused no change in the record. Records were taken in 3 instances within ten minutes of the time of injection, 2 of these being taken sixty seconds after the injection. In 24 instances records were made on the first or second day; in 11, on the third and fourth days; in 8, on the fifth and sixth days, and in 8, after the sixth day. The electroencephalogram was recorded from 1 animal four months after the injection. Figure 2 *B* summarizes the findings in the records of 19 dogs studied in this manner. One dog was excluded from this tabulation because of the presence of infection. The indexes were obtained by counting the waves in a thirty second, artefact-free sample selected as being representative, in each case, of a much longer recording.

The most noticeable alteration in the recorded electroencephalogram was the appearance of large delta waves (1 to 3 cycles per second at 20 to 60 microvolts) and the disappearance of the normal fast frequencies. This change was seen as soon as thirty seconds after the injection and was very noticeable in records taken on the first and second days after the lesion was made. Following this there was a gradual return toward the normal record, with a decrease in amplitude of all abnormal activity and the progressive disappearance of the delta waves, affecting the slowest waves first. After the seventh day the record appeared fairly normal to casual inspection, and in dogs seen from two weeks to four months after the injection the electroencephalogram could not be told from a preinjection record. Figure 2 *A* shows the typical sequence of electroencephalographic alterations as demonstrated by a dog in which 1.5 cc. of white wax–iodochlorol mixture

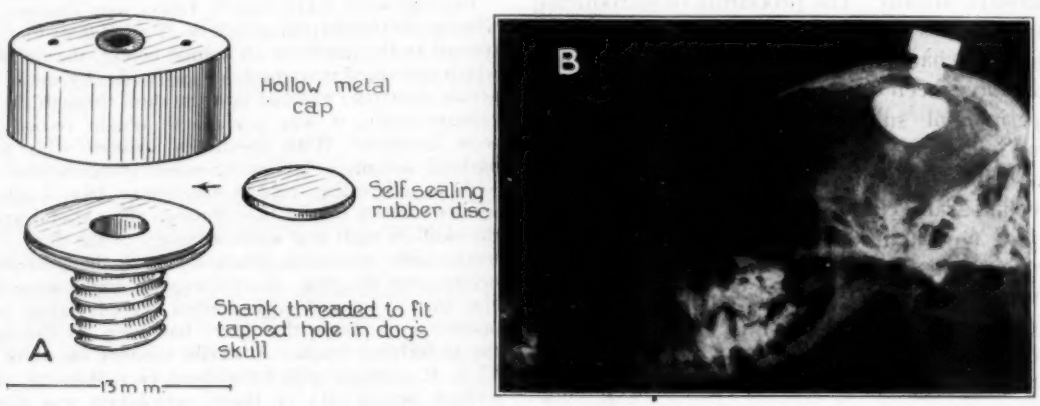

Fig. 1.—*A*, hollow, stainless steel plug designed to permit intracerebral insertion of space-occupying lesions. *B*, roentgenogram of dog's head, showing steel plug in position in the skull and intracerebral radiopaque mass which has been injected through it.

was injected just below the cortex. Bipolar recording from six electrodes placed linearly across the involved hemisphere permitted localization of the lesion by a focus of out of phase delta activity similar to the foci seen in electroencephalographic localization studies on human patients. In figure 3 *B* the type of electroencephalographic disturbance produced experimentally in the dog by the intracerebral injection of wax is compared with a similar disturbance which may be seen with intracranial neoplasm in the human subject.

In the early experiments some discrepancies in the sequence of electroencephalographic

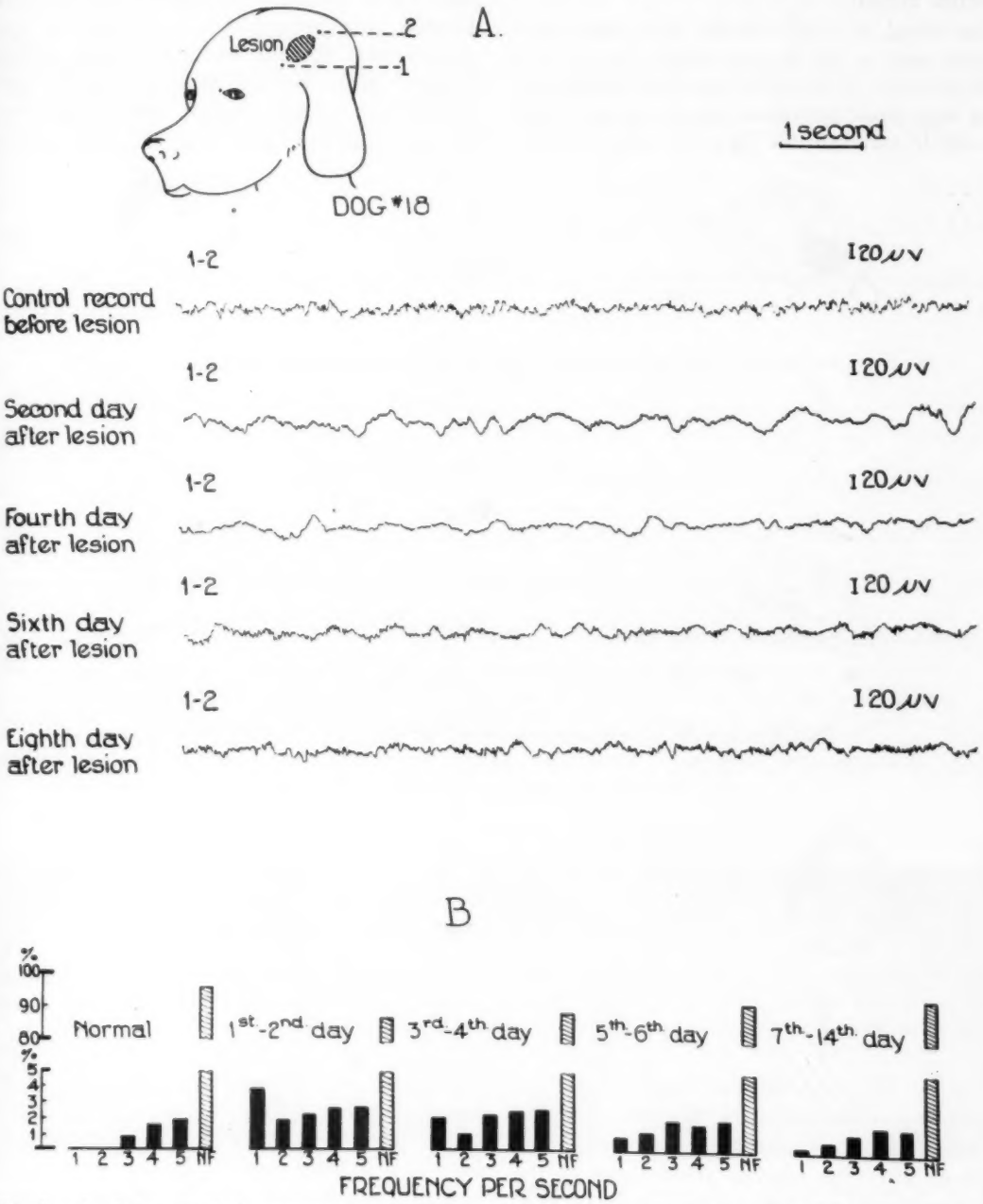

Fig. 2.—*A*, electroencephalogram as recorded from skull electrodes in a dog under local anesthesia with 1.5 cc. of wax mixture placed intracerebrally. The control record was taken just before, other records at intervals after, the injection. *B*, brain wave frequency spectrums determined by counting the waves in sample strips of electroencephalograms from 19 dogs with intracerebral lesions. The normal spectrum was determined from records taken before injection; the other spectrums, from records taken at intervals after injection of the intracerebral wax masses. The cross-hatched bar, *NF* (normal fast), represents all frequencies above 5 cycles per second, which make up the greater number of waves in the electroencephalogram of the dog when awake. (Note that the percentage scale is nonlinear.)

changes were observed. Later observations on the placement of electrodes through the scalp revealed that early occasional failure to record existing abnormalities could be explained by slight changes in electrode placement. A shift of electrodes, a distance as small as 5 mm., could mean the difference between a relatively normal and an abnormal record.

The initial injection of the wax–iodochlorol mixture used in the 20 dogs varied from 1 to 2 cc. in amount. Both white wax–iodochlorol and white wax–liquid petrolatum mixtures were used, in order to ascertain the chemical effect of iodochlorol on the electroencephalogram. Similar results were obtained with the two mixtures. Three dogs in the series were given additional injections after the original disturbance of the electroencephalogram had disappeared. In 1 of these animals the total intracerebral mass of 5 cc. caused death within twelve hours. In the other 2 dogs the additional wax again produced slow abnormal potentials in the electroencephalogram. In the infected dog the wax mass lay virtually within a brain abscess. The electroencephalogram of this animal was characterized by high voltage delta waves, which continued unabated until the death of the animal, four days later. Encroachment of this wax mass on the motor area occurred in 1 dog. In this animal there developed typical jacksonian convulsions, first observed twenty-four hours after the injection. These attacks were of five to forty seconds' duration and occurred every twenty to thirty minutes until the dog was killed, after six hours of observation. Records taken during this period showed rapid high voltage, spiking activity of the type that has been described in the electroencephalogram of patients during convulsive seizures. This activity was more marked on the side of the lesion. Postseizure recordings showed intermittent brief periods of cortical inactivity, and the interseizure records revealed delta activity, most pronounced on the side of the lesion.

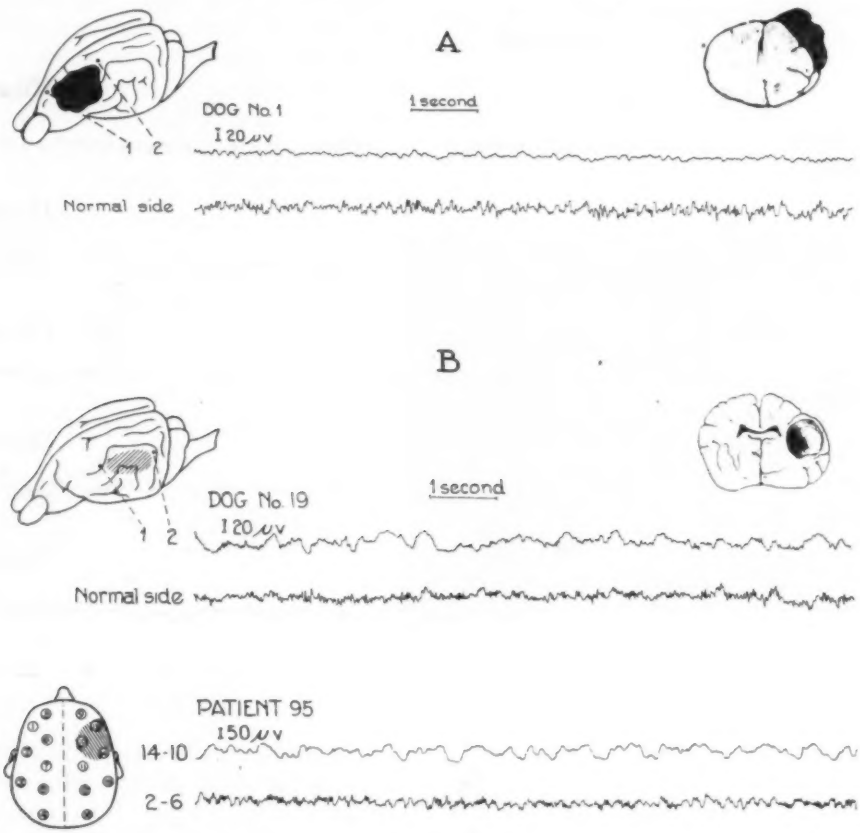

Fig. 3.—Electroencephalograms recorded simultaneously from the side of the lesion and from a homologous area on the normal side in (*A*) a dog with an extradural space-occupying lesion, and (*B*) a dog with an intracerebral space-occupying lesion and a patient with cerebral astrocytoma.

In dogs with intracerebral lesions the transient focal changes could still be detected in the electrocorticogram at a time when the record from electrodes in the skull revealed an apparently normal electroencephalogram. Leads from the

skull are much less efficient in detecting abnormal cerebral activity, as produced here in dogs, than are leads placed directly on the surface of the brain. Figure 4 A shows the striking difference between records obtained from the skull and those from the cortex ten days after injection. Cortical leads on tissue immediately adjacent to a point of injection exhibited alteration in the electrocorticogram (slow potentials and decreased amplitude of normal waves) one minute after intracerebral injections of wax. It was found that cortical recordings at points progressively removed from the lesion produced records which more nearly resembled the normal control record from the opposite side (fig. 4 *B*). It was found, however, that definitely abnormal records could be obtained at a distance from the injected mass with the electrode over brain tissue that appeared normal to both gross and microscopic inspection.

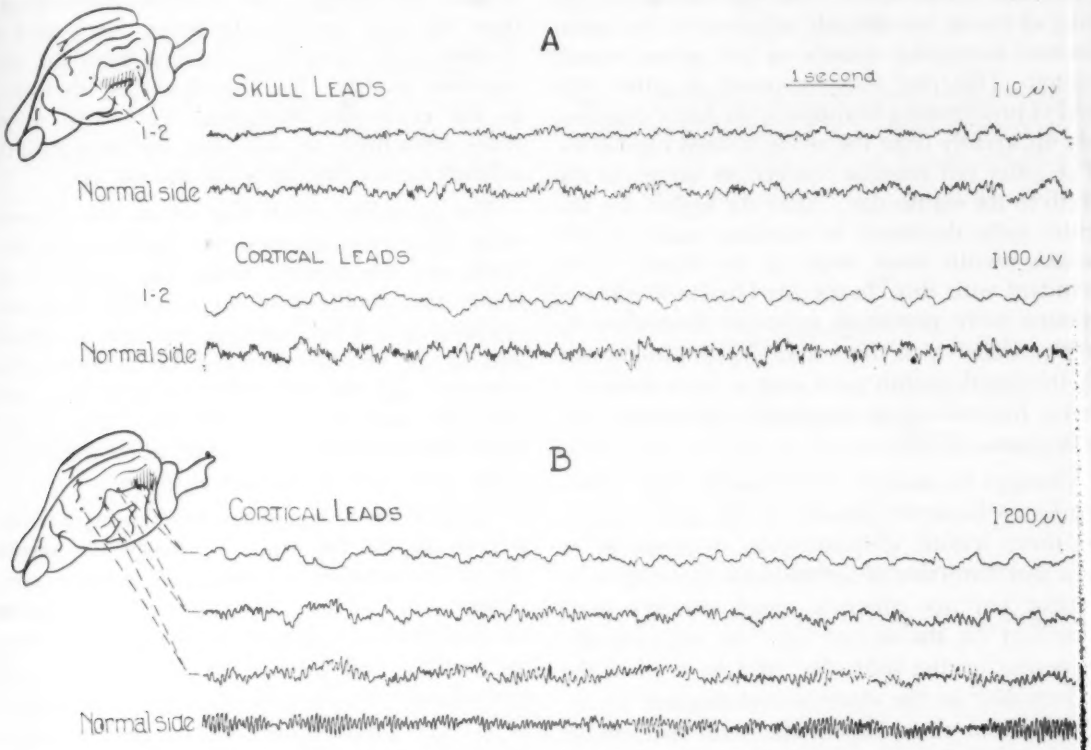

Fig. 4.—*A*, comparison of an electroencephalogram recorded from skull electrodes and records taken by cortical leading from an unanesthetized waking dog ten days after the placement of an intracerebral lesion, and at a time when the focal abnormality as seen with skull recording had nearly disappeared. *B*, brain potentials as recorded from the cortex of a dog under local anesthesia twelve days after production of an intracerebral lesion. The first three strips were recorded from successive pairs of electrodes on the side of the lesion. The fourth strip is from an area on the normal side, homologous to that from which the first strip was recorded.

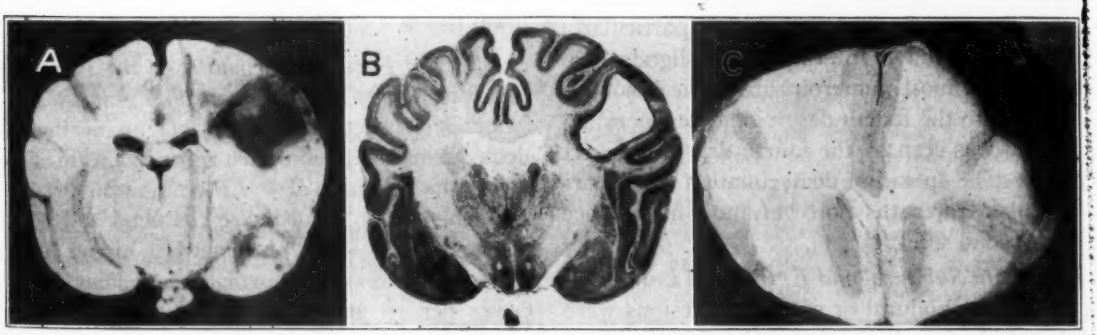

Fig. 5.—*A*, section through the brain of a dog with an intracerebral lesion; *B*, Nissl preparation of the same section; *C*, section through the brain of a dog with an extradural lesion.

Histologic preparations of the brains of dogs with intracerebral lesions (fig. 5 *A* and *B*) showed initially swelling of the brain tissue and a reacting zone of capillary proliferation, with perivascular appearance of polymorphonuclear leukocytes and lymphocytes. On the fourth day the ring of tissue immediately adjacent to the lesion showed increasing density on low power examination. This ring was composed of gitter cells and of proliferating fibroblasts, the latter originating apparently from the newly formed capillaries. The gitter cell reaction reached its height on the sixth to the eighth day. After the eighth day the gitter cells decreased in number, until by the fourth month none were to be found. Concomitant with this change the bipolar fibroblasts became more prevalent, arranged themselves in rows parallel with the borders of the lesion and by the fourth month were seen to have formed a dense, fibrous capsule completely surrounding the wax mass.

Changes in neurons were visible only where the lesion bordered directly on the gray matter. In these lesions chromatolysis, vacuolation of cells and distortion of architectonic layering were present but not common. Such changes were seen first on the second day but were equally numerous on the sixth day, at a time when the abnormality in the electroencephalogram as recorded from electrodes in the skull had almost disappeared. It was not possible to determine if these changes in the ganglion cells were reversible, as the number of damaged ganglion cells was small and evidence of dropping out of such cells at later stages of the process could not be detected. Some proliferation and swelling of astrocytes and increase in the number of microglia nuclei were seen in the neighboring gray matter, particularly after the third day. Interfascicular oligodendrocytes seemed most numerous about the lesion on the second to the fourth day. Some degeneration of myelin was seen by the fourth day in Weigert sections. The spread of demyelination along bordering fiber tracts was, however, more in evidence by the second week.

Dogs with Subdural and Extradural Lesions.—In 5 animals subdural or extradural lesions were produced incidentally to the study of intracranial lesions. Although the series is small, the findings are of interest and deserve a more thorough investigation. In these animals from 1 to 3.5 cc. of wax mixture was injected subdurally (2 dogs) or extradurally (3 dogs). Records were taken on these animals from thirty seconds to two days after the injection. With this type of lesion slow delta waves were not seen; instead there was a selective loss of the normal frequencies, fast and slow. In all cases the record from the site of the lesion appeared almost completely flat at an amplification that had previously been adequate for normal recording. The electroencephalograms from the side opposite the lesion were used as controls and showed no changes from the preinjection records. The aforedescribed alterations in the electroencephalogram were seen at all times, from thirty seconds after injection until the animals were killed, after the second day.

The possibility exists that simply the presence of an electrically inactive mass between the electrode and the cortical tissue can serve to decrease the amplitude of the recorded electroencephalogram. This, however, was not an important factor, because reduction of amplitude was observed with the electrodes placed on the cortex after the mass had been removed. Figure 3 *A* shows the electroencephalogram as recorded from a dog with such an extradural lesion.

Sections were made from these brains after the second day of the lesion. Grossly the section showed indentation and deformity of the cerebral cortex (fig. 5 *C*). Microscopic examination showed neuronal changes, including chromatolysis, swelling and vacuolation of cells on the side of the lesion. No demyelination was demonstrable in Weigert preparations, and no glial or mesenchymal reaction was seen in the brain substance. Although all histologic sections were from animals killed two days after the lesion was introduced, it seems reasonable to believe that changes recorded in the electroencephalogram as soon as one minute after the injection were not dependent on such histologically demonstrable alterations in brain tissue.

Effect of Focal Abnormality on the Brain Potentials of Sleep and Pentobarbital Anesthesia.—The electroencephalograms of unanesthetized dogs during sleep have been recorded in this laboratory incidentally to the investigation of other problems. Such records are characterized by the appearance of waves of somewhat higher amplitude and slower than normal frequencies (3 to 5 cycles per second) and by the disappearance of much of the normal fast activity. Two dogs in the present study fell asleep during the recording of the electroencephalogram. One of these animals had had wax injected intracerebrally thirteen days previously; the other had an extradural injection of wax mass two days before the record was taken. In both instances the characteristic sleep pattern was seen only on the normal side.

In both dogs the disturbance could be caused to disappear by awakening the animal, only to have it reappear again with the advent of sleep (fig. 6*A*).

The record of the dog under pentobarbital anesthesia characteristically consists of high voltage, irregular groups of waves of 5 to 10 cycles per second occurring against a background of waves of 3 to 12 cycles per second. Similar activity has been described in the cat.[10] For 7 dogs records were made with pentobarbital anesthesia from two to twelve days after intracerebral injection of wax mixture. In 2 cases the record was from scalp leads, and in 5 from the exposed cortex, as a terminal procedure in the experiment. A difference was observed between the normal side and the side of the lesion in all the dogs anesthetized with pentobarbital. The differences, however, were less marked than in the unanesthetized dogs. Spontaneous bursts of activity during pentobarbital anesthesia were of considerably less amplitude on the side of the lesion in some animals (fig. 6*B*).

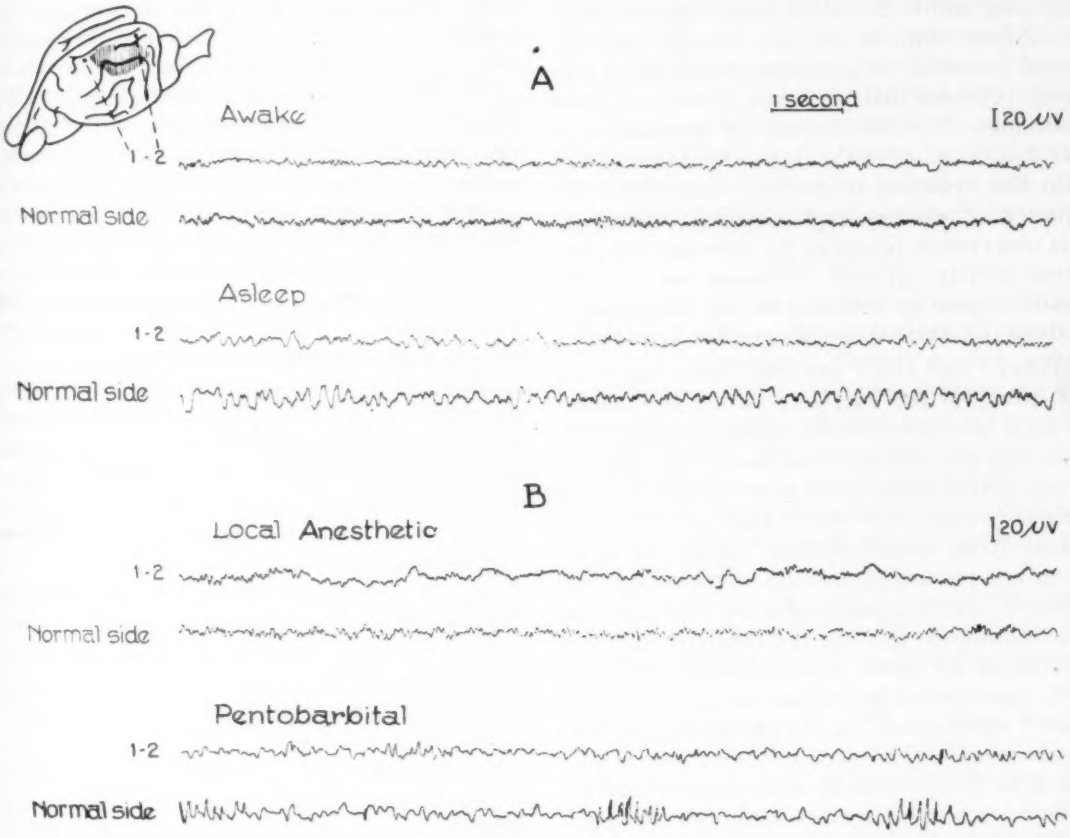

Fig. 6.—Electroencephalograms from skull electrodes in dogs with intracerebral lesions and with procainized scalp. (*A*) The upper records were taken with the animal awake. The lower strips, taken during sleep, demonstrate the relative absence of slow waves on the side of the lesion. (*B*) The upper record was taken when the dog was awake. The lower strips, taken after the intravenous injection of 3 cc. (200 mg.) of veterinary pentobarbital sodium (15 pound [6.8 Kg.] dog), show relative absence of spindles characteristic of pentobarbital anesthesia in records taken on the side of the lesion.

COMMENT

The mechanism of the production of abnormally slow brain potentials in cases of space-occupying intracranial lesions is not known. However, the presence of occipital and posterior parietal delta waves in cases of tumors lying entirely within the posterior fossa [11] points to some mechanism for production of slow waves other than the direct effect of neoplastic cellular metabolism. Furthermore, it has been shown by Murphy and

10. Morison, R. S.; Finley, K. H., and Lothrop, G. N.: Spontaneous Electrical Activity of the Thalamus and Other Forebrain Structures, J. Neurophysiol. **6**:243, 1943.

11. Smith, J. R.; Walter, C. W. P., and Laidlaw, R. W.: The Electroencephalogram in Cases of Neoplasms of the Posterior Fossa, Arch. Neurol. & Psychiat. **43**:472 (March) 1940.

Dusser de Barenne [12] that products of tissue destroyed by thermocoagulation have the effect of lowering the p_H and bring about a reduction of cortical activity. The present experiments illustrate well that the presence of inert intracerebral masses results in the appearance of slow waves from adjacent cerebral tissue. In this work the immediate appearance of abnormal potentials makes it seem reasonable to conclude that delta waves can occur apart from evident inflammation or edema as demonstrated by routine histologic study.

Although mechanical pressure from a foreign body lying within the white matter appears to be an adequate stimulus for slow activity, the abnormal potentials so produced soon tend to disappear provided that the lesion remains of fixed dimensions. Further increase of pressure at a later date (i. e., after the dog's electroencephalogram had returned to normal) reactivated the sequence of electroencephalographic alteration. This observation points to the necessity for continued activity (growth, irritation, etc.) of the causative agent as essential for the maintenance of abnormal electroencephalographic activity.

Walter [5] and other workers [6] have suggested that injury to the overlying cortex is essential for focal electroencephalographic abnormalities. Were this the case, it would seem that pressure on the cortical layers from above would be more likely to produce slow waves than pressure from a mass lying almost entirely within the white matter and producing pressure on the cortex only indirectly. In the experience of my associates and myself, however, this has not been the case, and pressure on the cortex from subdural and extradural experimental lesions and in certain clinical cases of meningioma has not produced high voltage slow waves. This is in contrast to the prominent delta activity seen by us in cases of cerebral astrocytoma and brain abscess and in experimental lesions in dogs when the lesion was placed within the white matter of the brain (fig. 3 *B*).

In the light of Kennard's [13] work, which showed that lesions in basal forebrain structures were productive of abnormal slow waves in the electroencephalogram, one must consider the possibility that delta waves seen in our experiments might have arisen from pressure on such structures. Examination of histologic preparations from the brains of our experimental animals, however, showed that such basal structures were not directly involved by these lesions.

It is seen from our experiments that surface compression eliminates cortical activity. It is our opinion that certain low voltage slow waves (4 to 8 cycles per second) without superimposed faster frequencies occasionally seen at the periphery of our subdural and extradural lesions may have been the result of sparing of the deep cortical layers, which presumably would be less affected near the borders of a surface compression. This opinion is in keeping with the observation that thermocoagulation limited to the outer cortical layers left a low voltage slow potential wave in the electrocorticogram.[14] Although these slow waves have been termed "delta-like,"[15] it seems to us that they may well be the low voltage slow component of the normal electroencephalogram which, in the intact cortex, combines with faster frequencies, presumably coming from more superficial layers of the cortex,[16] to give the full spectrum of the normal electroencephalogram. Such slow waves can be differentiated by their low amplitude and short wavelength from the high voltage delta discharge seen in dogs with intracerebral lesions.

The centripetal nature of the cortical blood supply renders it plausible that the diminished amplitude of cerebral activity seen in our experimental animals with subdural and extradural lesions could be explained on the basis of interference with the vascularity of the cortex. The intracerebral lesions, however, for the most part lay well below the gray matter and seemingly produced little disturbance in cortical circulation. Alterations in major channels of blood supply are therefore probably not an important part of the mechanism for the production of abnormally slow high voltage activity.

Kennard and Nims [17] studied cortical ablation in monkeys and found a nonspecific decrease in amplitude and frequency of electrical activity which paralleled the development of postoperative edema. These ablations are not entirely compar-

12. Murphy, J. P., and Dusser de Barenne, J. G.: Thermocoagulation of Motor Cortex Exclusive of Its Sixth Layer, J. Neurophysiol. **4**:147, 1941.

13. Kennard, M. A.: Effects on EEG of Chronic Lesions of Basal Ganglia, Thalamus and Hypothalamus of Monkeys, J. Neurophysiol. **6**:405, 1943.

14. Dusser de Barenne, J. G., and McCulloch, W. S.: Some Effects of Laminar Thermocoagulation upon the Local Action Potentials of the Cerebral Cortex of the Monkey, Am. J. Physiol. **114**:692, 1936.

15. Walter, W. G.: The Technique and Application of Electro-Encephalography, J. Neurol. & Psychiat. **1**:359, 1938.

16. Bishop, G. H.: The Interpretation of Cortical Potentials, in Cold Spring Harbor Symposia on Quantitative Biology, Cold Spring Harbor, L. I., New York, The Biological Laboratory, 1936, vol. 4, p. 305. Dusser de Barenne and McCulloch.[14]

17. Kennard, M. A., and Nims, L. F.: Effect on Electroencephalogram of Lesions of Cerebral Cortex and Basal Ganglia in Macaca Mulatta, J. Neurophysiol. **5**:335, 1942.

able to the space-occupying lesions studied here. On the other hand, their failure to find specific focal alterations may well have been due to the fact that the cortical leading in their acute experiments was performed with the animals under anesthesia, and that in their chronic experiments on unanesthetized preparations all records were taken from scalp leads. Anesthesia increases the difficulty of detecting focal changes resulting from injury, and we have observed in dogs under local anesthesia that electrocorticograms revealed focal abnormalities which were not detectable in the electroencephalogram taken with skull electrodes.

Kennard [18] studied dial-anesthetized monkeys after total decortication and observed ". . . 8-10 per sec. oscillations such as are normal in these animals." Obrador [19] found that the electroencephalogram was abolished by destruction of the hypothalamus in the cat under pentobarbital anesthesia. Such work has suggested that the electroencephalogram is dependent on subcortical structures. It is our opinion, however, that conclusions as to cerebral activity in anesthetized animals do not necessarily explain electroencephalographic phenomena in unanesthetized preparations. Even light barbiturate anesthesia produces an electroencephalographic pattern differing greatly from the electroencephalogram seen in normal, unanesthetized animals. Our own observations and those of Witwer and associates [20] suggest that interference with the afferent pathways to the cortex may eliminate certain potentials of sleep. We have also seen that subcortical lesions can in part abolish spindles associated with pentobarbital anesthesia from the electroencephalogram. Such evidence, therefore, seems to show that potentials directly dependent on deeper structures are only one component of the electroencephalogram. The electroencephalogram as recorded from the unanesthetized animal is in part dependent on activity in the cortex. Kennard's conclusion [18] that ". . . lesions confined to cortical tissue do not alter it [the electroencephalogram] even if an entire hemisphere is removed," has not been confirmed by our experience. This has been true both in the case of lesions causing pressure on the cortex and in the cases of a hemidecorticate dog and a congenitally hemidecorticate child that we have studied. In the latter cases our observations agree with those of Ten Cate and associates,[21] who found that the record from the normal side in hemidecorticate dogs, cats and rabbits was several times as great as that on the side of the decortication. Their experiments demonstrated that the cortex is essential for the normal electroencephalogram as recorded from the scalp.

In our experiments, pressure from within the white matter produced abnormally slow potentials of high voltage, whereas pressure on the cortical layers from without did not. It therefore seems that some alteration in fiber connections to the cortex may favor the appearance of slow activity, but it does not necessarily mean that the white matter is the point of origin for these potentials. It is possible that delta activity could arise either as a result of disturbance of afferent pathways to the cortex or from apparently reversible changes in cortical neurons, not demonstrable with common histologic methods.

CONCLUSIONS

High voltage slow (delta) waves were seen characteristically in the electroencephalogram of dogs with subcortical, space-occupying lesions. Such changes at their height resembled the electroencephalographic alteration seen in some cases of intracerebral, space-occupying lesions in man.

Disappearance of normal rapid activity and flattening of the electroencephalogram were seen with subdural and extradural space-occupying lesions in the dog.

Minor shifts in electrode placement can greatly alter the amount of abnormality seen in the electroencephalogram in cases of focal damage to the brain.

The electrocorticogram is a more sensitive record of abnormal brain potentials than is the electroencephalogram obtained by leading from the skull in dogs.

The electroencephalographic alterations caused by space-occupying lesions are of a reversible nature if the lesion is of fixed dimensions.

The electroencephalogram of the unanesthetized waking dog is in part of cortical origin. Brain potentials seen in sleep and during pentobarbital anesthesia may be controlled by subcortical mechanisms.

Harvard Neurological Unit, Boston City Hospital.

18. Kennard, M. A.: Electroencephalogram of Decorticate Monkeys, J. Neurophysiol. **6**:233, 1943.

19. Obrador, S.: Effect of Hypothalamic Lesions on Electrical Activity of Cerebral Cortex, J. Neurophysiol. **6**:81, 1943.

20. Witwer, E. R.; Derbyshire, A. J., and Corrigan, K. E.: Application of Some New Technics to Study of Brain Tumors, Radiology **41**:130, 1943.

21. Ten Cate, J.; Walter, W. G., and Koopman, L. J.: Electroencephalography After Removal of the Occipital Cortex, Arch. néerl. de physiol. **24**:153, 1939; Electroencephalography in Rabbits After Removal of Neopallium, ibid. **24**:578, 1940; Electroencephalography on Cats After Removal of Neopallium, ibid. **25**:27, 1940; Note on Electro-Encephalography of Brain Stem and Cerebellum of Cats, ibid. **25**:51, 1940.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Anatomy and Embryology

ANATOMIC VARIATIONS OF THE LATERAL AND SIGMOID SINUSES. JULES G. WALTNER, Arch. Otolaryng. **39**:307 (April) 1944.

Waltner reports a hitherto unknown anomaly of the sigmoid sinus.

A 65 year old patient was operated on for septic thrombophlebitis of the right transverse sinus, but the sigmoid sinus could not be located; the patient died of purulent meningitis due to pneumococci of type III, which originated from a deep epidural abscess of the right posterior fossa. Autopsy revealed the following anatomic features: The left lateral and sigmoid sinuses were large, ended in a large jugular bulb and produced a deep groove in the left occipital and temporal bones. The left superior and inferior petrosal sinuses were normal. The right lateral sinus was narrow and barely admitted a probe. The right sigmoid sinus could not be found, and there was no evidence of a groove in the temporal and occipital bones. The superior petrosal sinus was normal and connected the narrow lateral sinus with the cavernous sinus. The inferior petrosal sinus was wider than usual, communicated regularly with the cavernous sinus and laterally ended in a pouch, which occupied the place of the jugular bulb and opened into a narrow internal jugular vein.

The author points out that variations of the lateral and sigmoid sinuses are independent of each other because these structures are developed from separate anlages and at a different stage of fetal life. A normal sigmoid sinus or a normal lateral sinus may each be present with the other sinus absent. The sigmoid sinus shows greater constancy and fewer variations than does the lateral sinus. This could be explained by the fact that the lateral sinus has to adapt itself to the increasing size and changing form of the surrounding structures, for example, the brain and the otic capsule. Thus, the lateral sinus is more likely to be interfered with in its development than is the sigmoid sinus. The latter is located close to the base of the brain from the very beginning of its development.

RYAN, M. C., A. U. S.

Physiology and Biochemistry

THE ELECTROSHOCK CONVULSION SYNDROME. PAUL H. WILCOX, Am. J. Psychiat. **100**:668 (March) 1944.

Wilcox describes in detail the seizure picture encountered in electric shock therapy, dividing the seizure into (1) the tonic phase, (2) the clonic phase, (3) the atonic phase, (4) the stuporous period and (5) the postconvulsive mental state. He concludes that the electric shock convulsion is the result of integrated activity of a cortical area near the fissure of Rolando and is essentially a pyramidal tract syndrome. This conclusion is based on the following observations: (1) The most efficient shocks were those produced by stimulation near the fissure of Rolando; (2) the tonic pattern appeared to be the result of generalized excitation of the cortex, since there was a universality of muscular contraction; (3) a patient with a lesion of the pyramidal tract involving one leg had less strong contractions in that extremity, evidence that lesions of the pyramidal tract modify the seizure pattern; (4) disease of the extrapyramidal tract did not modify the convulsive pattern in a patient with all the classic signs of advanced postencephalitis; (5) autonomic excitation appeared to be a secondary phenomenon, since incontinence occurred not in the tonic or the clonic phase but in the stuporous period; (6) no simple medullary syndrome occurred, as indicated by changes in respiration and pulse; (7) strength-duration curves for threshold stimulation can be determined for electric shock, and (8) sodium amytal raised the convulsive threshold. Wilcox states that this drug acts primarily on the higher cortical levels of integration and concludes that the trigger zone is probably at a "fairly high level of cortical integration."

The author concludes that the trigger zone plays a central role in all convulsions and that epilepsy is due to an overflow of excess irritation from some other area. The complex character of convulsive patterns in epilepsy may be due to the modifying influence of the cerebral dysrhythmias.

FORSTER, Philadelphia.

THE STRUCTURAL IDENTITY OF THE PAIN SPOT IN HUMAN SKIN. G. H. BISHOP, J. Neurophysiol. **7**: 175 (May) 1944.

Bishop mapped the most sensitive points for evocation of pain on his own forearm. These areas were then studied by chemical or surgical denudation to various depths, followed by electrical stimulation, not only after denudation but during the course of regeneration. Epithelium was found to regenerate from the base of each hair follicle, and a nerve twig containing pain fibers approached the epithelium near each group of hair follicles. This twig was distributed to an area containing one pain spot. The extreme sensitivity of the central high point in a unit pain area may be correlated with its position directly over the pain twig. Thus, terminals of several fibers may be activated by a stimulus at one point. Bishop found that the growing ends of pain fibers in the skin are more sensitive to mechanical stimulation and less sensitive to electrical stimulation than are their final sensory endings. However, various qualifying features are concerned in the conditions under which the stimuli are applied. Dendritic fibers were observed to invade the regenerated epithelium at about the stage at which nerve fibers are approaching it and appeared first in the regions overlying the nerve twigs. Bishop states that it is not clear whether this indicates a functional relation or merely a relation to the stage of development of epithelium from the follicles. He notes that accounting for the uniqueness of individual pain spots on a structural basis does not explain the sensory localization of pain.

FORSTER, Philadelphia.

PROGRESSIVE ASCENDING PARALYSIS IN DOGS DUE TO DEFICIENCY OF A VITAMIN B COMPLEX FACTOR FOUND IN YEAST. SUSAN GOWER SMITH, Science **100**:389 (Oct. 27) 1944.

Smith reports her observations on 38 dogs which received a synthetic vitamin B complex–free diet, composed of casein (water and alcohol extracted), 40 per cent; sucrose, 36 per cent; cottonseed oil, 18 per cent; cod liver oil, 2 per cent, and mineral salts, 4 per cent. This diet was altered in the case of the positive control animals to contain 10 per cent dried brewers' yeast as a source of the vitamin B complex. The other animals had their vitamin B complex requirement met by administration of seven or eight of the following synthetic vitamins: (1) thiamine hydrochloride, (2) riboflavin, (3) pyridoxine, (4) nicotinic acid, (5) pantothenic acid, (6) paraaminobenzoic acid, (7) inositol and (8) choline.

The incidence of progressive ascending paralysis varied considerably with the different deficiencies, but it was greatest in the animals receiving all the synthetic vitamin B complex factors listed, 11 of the 12 becoming paralyzed. The paralysis was at first spastic and later became almost completely flaccid. The dogs died quickly if untreated.

Paralysis is regularly prevented by brewers' yeast and is cured by a water extract of yeast. It responded promptly (eight to twelve hours) to biotin therapy in seven attacks in 4 dogs. The biotin was dissolved in isotonic solution of sodium chloride U. S. P. and administered subcutaneously. The therapeutic dose is approximately 100 micrograms per kilogram of body weight.

GUTTMAN, Philadelphia.

THE CHEMISTRY OF CEREBRAL TUMOURS AND OF CEREBRAL CYST FLUIDS. J. N. CUMINGS, Brain **66**:316, 1943.

Cumings studied the water, potassium, sodium chloride and phosphorus contents of 47 tumors of the brain and of 5 tumors of the spinal cord, as well as the nucleoprotein, phospholipid and acid-soluble phosphorus contents of 38 tumors of the brain and the fluid of 26 cerebral cysts and 1 subdural hematoma. Of the tumors, medulloblastoma had the highest water content, and spinal chordoma the least. An elevated phosphate content of tumors appeared to be related to a tendency to degenerate. The amount of nucleoprotein varied, probably in accord with the degree of cellularity of the particular tumor. Nearly all the cysts contained a high concentration of acid-soluble phosphorus. A moderate amount of phospholipids appeared in most cysts, notable exceptions being the subdural hematoma, pituitary adenoma and suprasellar cyst. From these studies Cumings concludes that tumor cysts probably occur by breakdown of tumor and cerebral tissue.

FORSTER, Philadelphia.

PROPOGATION OF EPILEPTIFORM IMPULSES IN THE BRAIN: I. ROLE OF THE CORPUS CALLOSUM. SIXTO OBRADOR ALCALDE, Bol. d. Lab. de estud. med. y biol., Mexico **1**:29 (April) 1942.

Obrador Alcalde stimulated the cerebral cortex of cats with an alternating electrical current for periods of ten seconds at intervals of two minutes. The corpus callosum was sectioned in 11 animals. There was no significant change in the nature of the induced convulsive seizures after section. In only 1 animal were the convulsions less intense in the limbs ipsilateral to the side of the brain which was stimulated. In a few other animals there was some variation in the convulsive threshold with slight decrease in intensity of the convulsions. There was no significant variation in the pattern of the attacks. The corpus callosum therefore does not appear to be essential in transmission of epileptigenous impulses from one side of the brain to the other.

SAVITSKY, New York.

Neuropathology

SIMMONDS' DISEASE WITH THERAPEUTIC RESPONSE TO HORMONE THERAPY FOR FOUR YEARS: REPORT OF A CASE WITH NECROPSY FINDINGS. WARD DARLEY, ROBERT W. GORDON and KARL T. NEUBUERGER, Ann. Int. Med. **21**:890 (Nov.) 1944.

Darley, Gordon and Neubuerger report the case of a man who first came under their observation when he was 44 years of age. The results of clinical and laboratory studies were characteristic of Simmonds' disease, which had been present for twenty-three years. The administration of chorionic gonadotropin produced a therapeutic response for four years.

Necropsy revealed complete obliteration of the pituitary, pronounced sclerosis of the thyroid and testes and atrophy of the prostate and adrenals, together with moderate degenerative changes in the brain, particularly in the thalamus and the interbrain.

GUTTMAN, Philadelphia.

LATE CEREBRAL SEQUELAE OF RHEUMATIC FEVER. WALTER L. BRUETSCH, Arch. Int. Med. **73**:472 (June) 1944.

Bruetsch reports his observations in 500 consecutive and unselected necropsies on patients with mental illness. Rheumatic cardiovalvular changes were noted in 5 per cent of the subjects. Of the group of 171 patients with dementia paralytica, rheumatic valvular disease was present in only 1.7 per cent, while in 100 patients with schizophrenia the incidence was 9 per cent. Of 549 female patients admitted, 8.1 per cent had evidence of rheumatic infection. The incidence in 502 male patients was 2.6 per cent. The ratio of the incidence in men to that in women was approximately 1:3. It is estimated that there are about 1,000,000 persons with rheumatic heart disease in this country—or less than 1 per cent of the total population. The high prevalence of rheumatic cardiac disease among patients with mental illness suggests the possibility of a direct relation between rheumatic fever and mental symptoms.

Bruetsch states that a late sequel of rheumatic fever is obliterating endarteritis, which usually develops while the patient is otherwise in good health. This vascular process may produce gross and microscopic infarctions in the gray matter of the brain, with consequent mental symptoms. This change represents a chronic infectious process, similar to rheumatic heart disease, and has been termed "rheumatic brain disease." Other late cerebral sequelae of rheumatic fever are encephalitis and cerebral embolism, the latter occurring most often during auricular fibrillation in patients with mitral stenosis.

GUTTMAN, Philadelphia.

ENCEPHALITIS COMPLICATING VIRUS PNEUMONIA. HELEN INGLEBY, Arch. Path. **37**:359 (June) 1944.

In a patient aged 58 who died with symptoms suggestive of "acute encephalitis" complicating virus pneumonia, inclusion bodies similar to those described by Adams were found in the epithelium of the bronchi and

other organs. Numbers of them were noted in all parts of the brain—in the nerve cells, the neuroglia cells and the perivascular zones. Vascular thrombosis and acute degeneration of nerve cells were present. Perivascular exudate was not a feature of the disease.

WINKELMAN, Philadelphia.

MYASTHENIA GRAVIS. FRED S. PREUSS and SEABURT GOODMAN, Arch. Path. **37**:389 (June) 1944.

In a typical case of myasthenia gravis of about six weeks' duration in a patient aged 59 in which neostigmine was of no value, autopsy showed thymoma (marked hyperplasia of the thymus), hemangioma of the liver, a fibromyoma of the lower third of the esophagus, nodular hypertrophy of the prostate gland and neurofibromatosis. There is no similar case in the literature of a combination of neurofibromatosis and myasthenia gravis.

WINKELMAN, Philadelphia.

AMEBIC COLITIS COMPLICATED WITH ABSCESS OF THE BRAIN. BELA HALPERT and J. D. ASHLEY JR., Arch. Path. **38**:112 (Aug.) 1944.

Among the complications of amebic colitis, abscess of the liver is frequent, the incidence varying from 3.5 per cent, in living patients, to over 42 per cent, in patients with necropsy. Involvement of the brain is a rare complication and is usually associated with similar involvement of the liver and lungs or of both these organs. To date, 61 cases of amebic abscess of the brain have been reported. The case reported by Halpert and Ashley is the fifth in the literature in which abscess of the brain occurred without involvement of the liver and lungs.

WINKELMAN, Philadelphia.

THE CENTRAL NERVOUS SYSTEM IN DIPHTHERIA. A. B. BAKER and H. H. NORAN, J. Nerv. & Ment. Dis. **100**:24 (July) 1944.

The effects of diphtheria on the nervous system are due to the action of the powerful exotoxin elaborated by the bacillus. Toxic mononeuritis or multiple neuritis is a not uncommon neurologic complication, while involvement of the central nervous system is rare, appearing as toxic delirium, toxic encephalitis or hemiplegia, the paralysis being the result of vascular occlusion due to an embolus originating from a cardiac thrombus secondary to myocardial damage. Hemiplegia usually appears late in the course of the disease, during the third to the fifth week. The authors present the case of a man aged 64 who had had postdiphtheritic hemiparesis since the age of 12 years. At the age of 52 he had an acute confusional state; after he recovered from this, he was psychotic until his death, from a head injury, at the age of 64. Coronal sections of the brain revealed a large multiloculated cystic area involving the left parietal and temporal lobes.

CHODOFF, Langley Field, Va.

ALLERGIC BRAIN CHANGES IN POST-SCARLATINAL ENCEPHALITIS. A. FERRARO, J. Neuropath. & Exper. Neurol. **3**:239 (July) 1944.

Ferraro reports the case of an 11 year old white boy in whom seizures developed two weeks after an attack of scarlet fever. The seizure was followed by temper tantrums, and within a few months the patient became "dull, stupid, unable to think coherently, and was awkward with his hands." Six months after the illness with scarlet fever the lad was institutionalized. He was distractable and showed impairment of attention and comprehension, and tests of his intellectual ability indicated deterioration. Speech was slurred; the deep reflexes were overactive, and there was a coarse tremor of the outstretched hands. He became dull, retarded and unclean in his habits. Typhoid vaccine was administered on two occasions. Later in the course of the illness he had a febrile illness for eight days, with fever, incontinence, stupor and frequent nasal hemorrhages. Involvement of the central nervous system was indicated by nystagmus, bilateral internal strabismus, overactive deep reflexes, ankle clonus and intermittent twitchings of the right arm and leg. Later the arms became flexed at the elbows, and both feet exhibited a strong plantar flexion. There was increased tone of the muscles of the jaw, so that the mouth could not be opened. Repeated lumbar punctures revealed an elevated spinal fluid pressure and a colloidal gold curve of 5555220000.

During the last months of his illness tube feedings were necessary. The limbs became spastic, and there were constant nystagmoid movements of the eyes. A Babinski sign was present bilaterally. Pneumonia developed, and death occurred about fourteen months after the onset of the acute exanthematous illness.

Ferraro also mentions the clinical history of a case previously reported by Winkelman. Anatomic study of tissue in both cases revealed the presence of a perivascular reaction, which was both lymphocytic and histiocytic. Lymphocytes prevailed in the less involved areas, whereas in the more severely damaged regions lymphocytes were surrounded with collars of compound granular corpuscles. Mixed with the lymphocytes here and there, especially in the areas of most intensive reaction, were elements presumably of mixed hematogenous and histiocytic origin, having a tendency to fuse together.

One interesting feature of the exudate was the extension of the microglial reaction, which could be traced from the blood vessels within the surrounding nerve parenchyma. The reaction of the microglia passed through all stages of transition to that of the compound granular corpuscle. A stage worthy of mention in this transformation was the loss of reticular appearance while the protoplasm was still compact, although the cell assumed a polygonal outline. Also, the vascular and the perivascular reaction were unusually intense, and both hematogenous and fixed elements seemed to participate. At times edema and hemorrhage were observed. Thrombi, softening and necrosis were also present on occasion.

Ferraro mentions three possible explanations of the pathologic process: a true inflammation, a degenerative disease process or an allergic reaction (hyperergic inflammation). He is inclined to view the process as an allergic reaction.

GUTTMAN, Philadelphia.

Psychiatry and Psychopathology

CIVILIAN WAR NEUROSES AND THEIR TREATMENT. FELIX DEUTSCH, Psychoanalyt. Quart. **13**:300, 1944.

Deutsch reports on the activities and findings of the psychiatric clinic of the Boston Psychoanalytic Institute. The objective of the clinic is the treatment of mentally ill persons rejected by the armed forces and the development of an emergency psychotherapy based on psychoanalytic principles. Since October 1942 the clinic has accepted for treatment 61 patients—45 men and 16 women. Fifty per cent of the men were the youngest of the family, the only child or the single boy among girls. Five patients had an acute and 56 a chronic psychosis. The disorder of 26 patients was diagnosed as psycho-

neurosis, that of 15 as a character disorder, that of 10 as a psychosomatic disturbance and that of 10 as a borderline state.

The civilian war neurosis is a family neurosis, centered around the member directly involved in the service, who either is then the contagious member or becomes the target and victim of the neurotic reaction of the environment. The main obligation of the soldier is to be aggressive at the right moment with the proper weapons, in common with his comrades. The aggressive tendency can be directed against external objects. This process increases his morale; i. e., it diminishes his fear of danger from without. The civilian, also, must acquire morale, the will to resist aggression, and must develop hostile feelings against outside forces, without the possibility of putting them into action. These hostile feelings are cultivated and increased by restrictions, deprivations and frustrations, for all of which the enemy is held responsible, so that there is no escape and no permissible response except that which is inherent in morale. The war situation so influences each civilian that he struggles to become a man while some one holds him back or so that he resists becoming a man while some one pushes him. The central factor is the fear of his own aggression. Other persons involved act by contagion or as participants in the conflict. In short, the civilian becomes ill because he cannot acquire the new personality, viz., the demand for increased aggression, which is in conflict with inertia and the fear of acting out aggressive impulses which the war asks of him.

The treatment of civilian war neuroses has been divided into two parts. The patient is interviewed by the psychiatric social worker, who gathers the facts of the medical and social history and makes and maintains all contacts with members of the family and the referring institutions. The psychoanalyst has personal contact only with the patient. Two or three of the patient's relatives and friends are treated as patients by other analysts if they are seriously involved in the case. The psychotherapy is directed essentially toward the conflict between passivity and activity, hostility and peacefulness, aggression and submission. Success depends on the redistribution of the libidinal factors which produce narcissistic self esteem, the capacity to develop aggression, the ability to direct that aggression adequately and appropriately and the courage demanded by independency and activity.

PEARSON, Philadelphia.

THE PHYSICAL EXAMINATION OF TWO THOUSAND CASES OF NEUROSIS. H. G. MCGREGOR, J. Neurol. & Psychiat. **7**:21 (Jan.-April) 1944.

Of 2,288 consecutive patients admitted to a military hospital, McGregor found that 3.4 per cent showed evidence of organic disease which was mistaken for a neurosis. In the remaining 2,210 patients the organic element was minimal. Of these, the patients with psychosomatic neuroses form the main consideration in this paper. In 14 per cent of these patients the blood pressure showed systolic and diastolic readings greater than 140 and 90 mm. These readings, however, were reduced to approximately normal with rest and confidence, except in the cases of 7 patients in whom abnormalities were discovered on examination of the retina and urine. There was no relation between the height of the blood pressure and the degree of anxiety. Of 150 men with symptoms of the effort syndrome, 29 showed a deceleration rate in excess of three minutes, but in every case a normal exercise tolerance was recorded. The increased deceleration rate was probably the result of emotional factors. The specific location of psychosomatic symptoms is influenced by physical and psychologic factors. Only the former were analyzed, with the following results: (1) Heredity: Once a neurosis became established in a family, succeeding generations tended to suffer from a similar one. (2) Constitution: Seventy-one per cent of the patients with psychosomatic disturbances showed a fundamental timidity or apprehensiveness in their output of physical energy, which had existed all their lives. (3) Incidence of previous disease or trauma: Antecedent disease played a large part as a predisposing factor, while remote trauma was common, particularly in cases of backache and headache, the localization of the neurotic symptoms being usually in the same position as the trauma. (4) Physique-personality: Although no systematic study was undertaken by the author, these factors were considered of significance in the specific clinical picture. All these factors were regarded merely as directing the location of the symptoms once the ultimate causes of the neurosis had produced a favorable psychologic status.

MALAMUD, Ann Arbor, Mich.

Meninges and Blood Vessels

CAVERNOUS-SINUS THROMBOPHLEBITIS — REPORT OF A CASE WITH MULTIPLE CEREBRAL INFARCTS AND NECROSIS OF THE PITUITARY BODY. AVERY D. WEISMAN, New England J. Med. **231**:118 (July 27) 1944.

Weisman reports the case of a 13 year old boy in whom thromophlebitis of the cavernous sinus developed subsequent to a furuncle on his nose. During the course of the illness, a total of twenty-four days, the patient exhibited edema about the left eye with proptosis. He was comatose much of the time. When aroused, he understood simple commands but was unable to speak. There was right hemiplegia with overactive deep tendon reflexes and an equivocal Babinski sign. Also, right homonymous hemianopsia was present, and funduscopic examination revealed edema and hyperemia, with blurring of the nasal margins of the disks. There was no response to painful stimuli over the right side of the face. The patient had one generalized seizure. The cerebrospinal fluid was under increased pressure and was yellowish and cloudy, and the white cell count was 2,900 leukocytes, of which 1,450 were polymorphonuclear leukocytes and 750 were erythrocytes. The total protein measured 534 mg.; the sugar, 57 mg., and the chlorides, 639 mg. per hundred cubic centimeters. A hemolytic Staphylococcus aureus was grown from the spinal fluid, as well as from the blood. Sulfadiazine therapy was of little avail, and trephination on the left side failed to reveal evidence of a subdural abscess. The patient died twenty-four days after the onset of his illness.

The significant findings at necropsy were as follows: thrombophlebitis of the left and right cavernous sinuses, the left superior petrosal sinus and the ophthalmic veins; bilateral orbital abscesses; basilar purulent leptomeningitis; infarction of the pituitary gland; small, recent cerebral infarcts, involving the left frontal, parietal and parieto-occipital lobes; cerebellar pressure cone; internal hydrocephalus; fibrinopurulent pleuritis with empyema (right).

Although several thrombosed arteries were found, no source of the thrombosis could be ascertained. The

pathologic findings provide an explanation of the clinical picture. The possibility of hypopituitarism as a sequel of thrombophlebitis of the cavernous sinus is suggested.

GUTTMAN, Philadelphia.

Diseases of the Brain

BRAIN LESIONS ASSOCIATED WITH EXPERIMENTAL "EPILEPTIFORM" SEIZURES IN THE MONKEY. S. EUGENE BARRERA, LENORE M. KOPELOFF and NICHOLAS KOPELOFF, Am. J. Psychiat. **100**:727 (May) 1944.

Barrera, Kopeloff and Kopeloff report the neuropathologic findings in Macacus rhesus monkeys in which convulsive seizures had been induced by a single application to the cerebral motor cortex of chemical and immunologic agents. With this technic, the authors induced not only acute manifestations but a state of chronic convulsive reactivity. Application of the agents produced a chronic progressive meningocortical scar. The scars developed in animals which had exhibited seizures as well as in those which had not had convulsive manifestations. The degree of pathologic alteration could not be correlated with the development or frequency of seizures. Barrera, Kopeloff and Kopeloff conclude that the pathologic changes produced were insufficient in themselves to account for the convulsive manifestations.

FORSTER, Philadelphia.

SPASMODIC TORTICOLLIS. RALPH M. PATTERSON and SAM C. LITTLE, J. Nerv. & Ment. Dis. **98**:571 (Dec.) 1943.

Patterson and Little review the literature and present new data on the subject of spasmodic torticollis based on a study of 103 cases of the condition. The muscles most commonly involved are the sternocleidomastoid on the side opposite the deviation and the trapezius muscle and the deep muscles of the neck on the same side. Usually muscles on both sides of the neck are implicated. The pathways concerned with mediation of the abnormal movements are probably in the vestibular and the extrapyramidal systems while in certain cases in which pronounced reflex synergism among the muscles of the hand, neck and eye is shown, tracts originating in the inferior olivary and the dorsal accessory olivary nuclei may be concerned.

The average age of onset was 37.8 years, and in 72 per cent of cases the appearance of symptoms was insidious. Pain was a frequent complaint, appearing in 66 per cent of cases. The importance of the "antagonistic gesture" in relieving the spasm was borne out in the study, and the authors believe that proprioceptive impulses from the arm used in the movement were of more importance than the side of the chin or the face to which the stimulus was applied. The disorder was influenced by numerous stimuli of various types. Sleep almost invariably abolished the spasms, while emotional stress aggravated them.

Neurologic abnormalities were present in 48 per cent of the cases. Changes in the cranial nerves, reflexes and sensations were all present. In only 6 of the 21 cases in which psychiatric evaluation was carried out were the findings considered significant. Lesions of the cervical vertebrae and cervical muscles were considered to be either incidental or secondary, while vestibular disorders appeared to be of significance in certain cases. In 5 of the cases there was a definite antecedent history of encephalitis.

The authors found that, contrary to common belief, the course of the disorder was not invariably progressive. A surprising number of patients showed considerable improvement or arrest of the condition.

Necropsy reports have failed to reveal any specific localization for the lesions responsible for spasmodic torticollis. The etiologic factors in the condition have been much debated, with the adherents of psychogenic and those of organic causation in disagreement. The authors feel that organic causes were paramount in their cases, and they minimize the importance of psychogenic factors. They feel that the pathophysiologic substratum of the disorder is basically in the extrapyramidal connections, with the vestibular mechanisms acting as a conditioning component. A combination of lesions is probably necessary, such as destruction of portions of the extrapyramidal system as a result of encephalitis and vestibular involvement, such as may accompany otitis media.

Methods of treatment have included use of mechanical restraints, heat and massage, electrical stimulation and galvanism; removal of foci of infection; administration of drugs, and psychotherapy. All of these measures were largely unsuccessful in the cases reported. Surgical treatment ranged through tenotomy of the sternocleidomastoid muscle, section of the spinal accessory nerve, multiple myotomy of the cervical muscles and rhizotomy of the posterior divisions of the upper cervical nerves. The procedure of combined bilateral extradural rhizotomies and section of both eleventh nerves has been successful in some cases. The method most commonly used at present was originated by Dandy and consists of bilateral section of the first, second and third anterior and posterior cervical nerve roots plus peripheral section of both spinal accessory nerves.

CHODOFF, Langley Field, Va.

ARTERIOVENOUS ANEURYSM OF MIDBRAIN AND RETINA, FACIAL NÆVI AND MENTAL CHANGES. R. WYBURN-MASON, Brain **66**:163, 1943.

Wyburn-Mason gathered from the literature 27 cases of retinal arteriovenous aneurysm or similar anomalies and found that in 22 of them there was evidence of an intracranial arteriovenous aneurysm. In the 14 of the 22 cases in which it was posssible to draw deductions the intracranial lesion was thought to be in the midbrain. Of the 20 cases of arteriovenous aneurysm, which included 6 of the series of 9 cases the author reported, retinal abnormalities were present in 14. When the condition was fully developed, the abnormal vessels extended from the retina as a tract of reddish vascular tissue on one side, covering and permeating the optic nerve, chiasm and tract and lying above the cavernous sinus. The mass of abnormal vessels extended posteriorly to reach the dorsum of the midbrain and permeated the quadrigeminal bodies, the brachia conjunctiva and the red nucleus. The mass of vessels sometimes extended anteriorly into the hypothalamus and the pulvinar, posteriorly into the cerebellum or laterally into the choroid plexus. Histologically, the affected portions of the brain consisted of many tortuous and dilated blood vessels, having the appearance, for the most part, of arteries. In these vessels degenerative changes sometimes occurred, particularly in the intima and elastica. Hydrocephalus was observed in all cases in which autopsy was done. There was an increase in the size and number of the blood vessels of the skull. Proptosis usually occurred in the affected eye. The vascular lesion of the eye was usually ipsilateral to the lesion in the midbrain and consisted of a direct arteriovenous communication, most frequently in the inferior temporal vessels. Vascular nevi were described in

several cases; they were usually in the trigeminal distribution and always ipsilateral. Other congenital anomalies were present in a number of cases. The anomalous vessels were considered of congenital origin. Wyburn-Mason correlated the development of the cerebral vascular system, as described by Streeter, with the development of this condition, concluding that any inherent defect of the vessels of the mesenchyme at Streeter's third stage would affect the vessels of the brain stem, retina and skin of the face.

Wyburn-Mason found that symptoms occurred in almost every case before the age of 30 and that the condition was slightly more common in males. The appearance of symptoms depends apparently on thrombosis or hemorrhage in the anomalous vessels; either visual or cerebral symptoms may be the first manifestation. Visual failure may be sudden or gradual. The lesions in the midbrain may give rise to a variety of symptoms, including subarachnoid hemorrhage, hydrocephalus or symptoms referable to the midbrain. Whatever the mode of onset, there is always evidence of a lesion in the midbrain, and the Weber syndrome predominates in frequency. Other cranial nerves or structures of the midbrain may be involved, however, and in some cases attacks resembling diencephalic fits occur. In late cases signs of arteriovenous aneurysm appear. Psychosomatic symptoms were divisible into temporary and permanent. Temporary symptoms include delirium, hallucinosis, disorientation, malaise and sleep disturbances. Permanent mental symptoms were divisible into disturbances of memory and intelligence and psychiatic reaction types. In some instances there was an increase in the pressure of the cerebrospinal fluid, and in most instances the total protein was elevated. Roentgenograms of the skull are usually normal but may show evidence of increased pressure, erosion of the apex of the petrous bone or shift of the pineal body. Air studies may reveal generalized hydrocephalus or yield evidence of a local tumor. Arteriography may give some indication of the nature of the pathologic process. Seven of Wyburn-Mason's 9 patients died. Roentgen therapy was found to be of no avail. Surgical treatment and the application of radon seeds to the sclera resulted in some improvement.

FORSTER, Philadelphia.

BLAST INJURY: NON-FATAL CASE WITH NEUROLOGICAL SIGNS. OLIVER GARAI, Lancet **1**:788 (June 17) 1944.

Garai reports the case of a young soldier thrown a few feet along the pavement by the blast of a bursting bomb. He had no appreciable external injury and did not lose consciousness or show retrograde amnesia; it was thought therefore that he had not suffered a concussion. At first the only neurologic sign was a dilated right pupil, which did not react at all to light and only slightly in accommodation. Two or three days after the accident an extensor plantar response developed on the left side, but he was well clinically. He lost the extensor response in two weeks; but the pupil was still sluggish in reaction to light a year later, although the response in accommodation had returned almost at once.

The spinal fluid was normal in all respects. The electroencephalogram showed a dominant 9 per second frequency of moderate voltage forty-eight hours after injury, with diffuse minor irregularities of rhythm in all areas, particularly a 4 to 6 per second frequency in the parietal region. In the following days and weeks, a slow rhythm appeared in the left frontal area and then gave way to small bursts of slow activity in all areas, with less evidence of a single focus. A year later this rhythm still persisted.

The author believes, since there was no concussion, that "the intracerebral lesion is best explained on the basis of altered hydrostatic pressure in the cerebral veins due to blast effects on the trunk." Thus, the changes in the right pupil and the signs referable to the pyramidal tract on the left side suggested a periaqueductal lesion in the midbrain, "possibly hemorrhagic."

MCCARTER, Philadelphia.

PAROXYSMAL AND POSTURAL HEADACHES FROM INTRAVENTRICULAR CYSTS AND TUMORS. WILFRED HARRIS, Lancet **2**:654 (Nov. 18) 1944.

Harris reports 3 cases of pedunculated tumor blocking one foramen of Monro, associated with sudden paroxysmal headache on change of posture of the head. Even more striking was the sudden relief of the paroxysmal headache with change of posture. The author stresses the character of the headache and the suddenness of its onset and disappearance, especially if changes of posture produce or relieve the headache suddenly, as diagnostic signs of a valvular intraventricular lesion. He emphasizes the fact that in many recorded instances, and in his own observations, cysts and tumors of the third and the lateral ventricles give no physical signs beyond the so-called classic triad of headache, vomiting and papilledema. It is therefore probable that in many such cases no autopsy has been done and that the incidence of these lesions is much greater than the published records indicate. Harris concludes that intermittent headaches, sometimes persistent for ten years, may be due to an intraventricular cyst or tumor. The onset and disappearance of the headaches are often sudden, and the sudden production or relief of headache with change of posture is a pathognomonic sign of the ball-valve action of such cysts or tumors in blocking one or both of the foramens of Monro. Colloid cysts of the third ventricle appear to be the commonest variety and grow from the anterior part of the roof of the third ventricle. They are nonmalignant, and, when approached through a hypophysial flap, they are not difficult to remove completely.

YASKIN, Camden, N. J.

Cerebrospinal Fluid

SOME OBSERVATIONS ON THE CEREBROSPINAL FLUID IN CLOSED HEAD INJURIES. J. H. PATERSON, J. Neurol. & Psychiat. **6**:87 (July-Oct.) 1943.

Paterson investigated the cerebrospinal fluid in 300 cases of acute closed head injuries uncomplicated with extradural or subdural hematoma. In nearly two thirds of the cases the cerebrospinal fluid pressure was normal, but there was a relatively higher proportion of cases of the more severe injuries in which the pressure was increased. In such cases there was a natural return to normal levels within one week of injury. These observations indicate that the pressure does not play an important role in the symptoms of acute injury. In 120 of the 300 cases blood in significant quantities was found in the cerebrospinal fluid at the initial puncture, but the clearance of blood was completed within one week of injury without repeated punctures, and the latter did not hasten the rate of clearance. The frequency of blood in the spinal fluid was directly proportional to the severity of the injury. No definite correlation existed between the level of pressure and the red blood cell count except when considerable bleeding had occurred, in which case there was usually a rise in pressure. There was a fairly close, but not invariable, relationship between the amount of blood in the cere-

brospinal fluid and the mental state of the patients. Alterations in consciousness were attributed by the author either to hemorrhage from cortical lacerations or to interference with the function of the midbrain.

MALAMUD, Ann Arbor, Mich.

Muscular System

MYOTONIC DYSTROPHY. B. B. MONGILLO and MAX SEROG, J. Nerv. & Ment. Dis. **99**:906 (June) 1944.

Mongillo and Serog review the literature on myotonic dystrophy. This condition differs from Thomsen's disease in the restriction of the myotonic reaction to a few muscles, the development of atrophies, the appearance of the disorder after the age of 30, the decreased strength or absence of tendon reflexes and the presence of extramuscular phenomena, such as cataract, testicular atrophy and baldness. In some cases the presence of tabiform ataxia has been correlated with degeneration of the posterior column. The myotonia tends to precede the development of the selective atrophy of the facial muscles, the sternocleidomastoid muscles, the muscles of the forearm and thigh and the dorsiflexors of the feet. Electromyographic studies have revealed the persistence of action currents after the cessation of voluntary muscle contraction, thus indicating the neurogenic, rather than the myogenic, nature of the disorder. Harvey has suggested that the favorable effect of quinine is due to a curare-like action, which decreases excitability of the end plates. In cases of atrophic myotonia associated with testicular atrophy, the use of testosterone propionate, in addition to quinine, has been favorably reported on.

The authors report a typical case of atrophic myotonia which they had under observation for more than a year. After treatment with a combination of calcium, quinine and thyroid had proved ineffective, the patient was given a preparation of vitamin E (1 capsule three times a day), to which weekly injections of testosterone propionate were later added. Under this regimen his general condition and the function of some muscles were considerably improved. This finding suggests the reversible nature of some of the neuromuscular disturbances characteristic of the disease.

CHODOFF, Langley Field, Va.

Congenital Anomalies

HEREDITARY ECTODERMAL DYSPLASIA. FRANCIS E. BRUNO and HUGO T. ENGLEHARDT, Ann. Int. Med. **20**:140 (Jan.) 1944.

Bruno and Englehardt report the case histories of 3 siblings with sparse hair of a fine texture and with nails of the fingers and toes which were short, thin and brittle and possessed a central concavity. In 2 of the cases the upper third molars were missing. The cases were regarded as examples of hereditary ectodermal dysplasia.

GUTTMAN, Philadelphia.

PARTIAL ALBINISM AND NYSTAGMUS IN NEGROES. L. J. A. LOEWENTHAL, Arch. Dermat. & Syph. **50**:300 (Nov.) 1944.

Loewenthal presents the case histories of 2 male Negroes with partial albinism. One was a "red" and the other a "yellow" Negro. Nystagmus of the congenital type was present in both patients. Nystagmus in albinos is not caused by gross deficiency in the eye, for each of the subjects had an amount of ocular pigment equivalent to that of a European brunet.

GUTTMAN, Philadelphia.

Book Reviews

Handbook of Psychiatry. By Louis J. Karnosh, B.S., ScD., M.D., and Edward M. Zucker, A.B., M.D. Price, $4.50. Pp. 302. St. Louis: C. V. Mosby Company, 1945.

The authors of this handbook are substantially faithful to their stated purpose expressed in the preface, namely, that this book is "a valuable increment of the library of the physician and the medical student." The integration into the practicing physician's armamentarium of the modern concepts in the field of psychiatry will enhance his diagnostic, as well as his therapeutic, skill.

The chief merit of this book is in its comprehensive coverage, as well as in its simplicity and clarity of presentation.

Compressed into brief chapters are the salient features of such subjects as "Heredity and Mental Disease," "Structure of Personality" and "Defense Mechanism of Personality."

Uniquely, there are included such provocative discussions as the chapters on "Psychosomatic Medicine" and "Mental Hygiene." The latter subject, although dealt with somewhat tentatively, opens a vast field for exploratory investigation, with promises of fruitful results. It is impressive that the sociologic and environmental factors in early development are recognized as determinative of future mental patterns.

The sections on "Neuroses and Psychoses of War" and "Physical Therapy," as well as the section on "Occupational Therapy," are particularly timely.

The up-to-dateness of the book is evidenced by the inclusion of discussions of such modern technics in therapy as electric shock and the use of penicillin in treatment of neurosyphilis.

Of course, one cannot expect within the limits of this book and its ambitious scope, exhaustive treatment of any one subject. However, for readers who may be interested in a more thorough understanding of any part of the text, the authors have furnished excellent references and authorities.

I believe that this book is a welcome contribution to the growing psychiatric literature.

Society Transactions

PHILADELPHIA PSYCHIATRIC SOCIETY

HAROLD D. PALMER, M.D., *President, in the Chair*

Regular Meeting, Nov. 10, 1944

Psychologic Factors in the Problem of Obesity. DR. ROBERT R. SCHOPBACH and DR. ROBERT A. MATTHEWS (by invitation).

This paper is a preliminary report indicating some general psychologic trends observed in a group of 50 patients studied by the endocrine clinic group of the Jefferson Hospital. The endocrine, chemical, anthropometric, roentgenographic, psychometric and psychiatric aspects were investigated, but only the study of the psychiatric factors disclosed any material of clinical significance. In all but 5 or 6 patients psychogenic factors bore a close relationship to the onset and development of obesity. Since the group was so small, statistical analysis was not attempted, but certain type reactions were noted.

Mild anxiety states with much neuromuscular tension and some obsessive-compulsive tendencies were most common. Patients with such states, who described themselves as "the nervous type," usually suffered an additional trauma, such as worry over a son going overseas, a husband coming home drunk or some incident which threatened their security. Under such conditions there may be an increased urge to eat; and unless the urge is satisfied, the tension mounts and other somatic symptoms appear. In some cases this process was repeated at short intervals for weeks or months, while in others it occurred only after some particular stress. In some cases there was a more specific trauma, arising from the family constellation, pubertal problems, sexual maladjustment, pregnancy or the climacteric.

Many of the patients were vaguely aware of the relation between their desire for food and their nervous tension. Most, however, were unable to use that knowledge but required psychiatric help before they were able to remain comfortably on a diet. For some patients minimal psychotherapy was helpful. Ideally, however, repeated conferences are required.

DISCUSSION

DR. ROBERT A. MATTHEWS: When the study of obesity was instituted at Jefferson Hospital, a psychiatric survey was made. It was expected that emotional problems would be found in a fairly large percentage of patients, but it was a surprise to discover that most of the patients showed such disturbances. All but 5 or 6 of the 50 patients presented some state of nervous tension, if one may use that term loosely, which seemed to have a relation to the intake of food. Most of these patients did not show what might be called an active or a clinically demonstrable psychoneurosis. When they were told by the physicians in the endocrine clinic that they should go to the psychiatric clinic, they remonstrated, saying, "I am not crazy; why do I have to go there?" When they came, they readily took an interest in the discussion of whether or not there was any relation between their nervousness, as we chose to call it, and their food intake. Again and again, the patient said "I am a nervous type; I feel better when I take food." In tracing the cause, we usually found one or another precipitating factor for anxiety. One group, which was not mentioned in the paper, was made up of a small number of patients who felt frustrated by life. "Why should I not eat? My husband comes home drunk every night. I can't stand him when he is that way. He never gives me money for any pleasure. So I eat. It is my only outlet." Such a patient is difficult to treat because there is not much that can be offered her. Other patients showed restlessness, with certain compulsive urges to partake of food. A psychiatric approach to the problem seemed to be of benefit. We feel that if the treatment of obesity is to succeed, most patients must have mental support. They must be kept under observation; otherwise they slip back into their old patterns. A few psychiatric interviews were helpful in a number of cases. In others lack of intelligence complicated the problem.

DR. H. D. PALMER: Another interesting phenomenon was the tremendous increase of weight noted in the patients with schizophrenia who had been subjected to frontal lobotomy. Such patients have lost anxiety and all nervous tension and show complete and utter relaxation. It would seem that in such a situation there is a release of inhibitory function which allows the patient to have a terrific appetite and to satisfy it. Five schizophrenic patients who had been underweight and who had undergone frontal lobotomy had an average gain of weight of 45 pounds (20.5 Kg.).

DR. ROBERT A. MATTHEWS: I don't know that I can answer the question as to why some patients who are anxious and tense lose weight and others gain, for there are certain problems yet not settled. The explanation may be related to the balance between energy intake and energy output and to body metabolism. In schizophrenic patients who gain weight after lobotomy there are a general quieting down and a flattening of the affect, as well as a blunting of social sensibility, which results in bad table manners and possibly in a tendency to eat too much. It is still not known why some people can eat a great deal and remain thin while others eat less and become fat. The physiologists will have to help with an explanation.

DR. J. C. YASKIN: I should like to get a clearer idea of the relation of anxiety states and the appetite. I have not seen patients with real anxiety who became fat. Except for the psychoneurotic patients who have a compulsion to eat, persons with anxiety states do not as a rule lose their anxiety with increased food intake. The patient with an involutional psychosis does not usually gain weight.

In questioning patients concerning possible conflicts responsible for their condition, one must follow the law laid down by Dunbar: It is not the presence of conflictual material that determines the production of symptoms but, rather, the reaction to that conflictual material. Any survey of large numbers of patients will give evidences of emotional conflict which may or may not be related to the symptom under scrutiny.

DR. ROBERT A. MATTHEWS: The tendency to read into something what is not there must always be guarded against. As a matter of fact, my colleagues and I asked ourselves whether we were suggesting possible factors to these patients and whether we were misinterpreting our observations or putting two things together which did not logically belong there. We tried to be as objective as possible. Perhaps we did sometimes put two things together which did not belong in the same category, but it was interesting to note how often the patient would produce material which seemed to represent his own observations on the relationship between nervous tension and eating habits. We did not see clearcut severe anxiety states in this group. I agree with Dr. Yaskin that patients with nervous tension do not as a rule gain weight unless there is a strong compulsion to eat. Compulsive tendencies were displayed by a good many of these patients.

DR. ROBERT R. SCHOPBACH: In a few cases, we found that gains in weight occurred soon after episodes which produced tension and that as tension was allayed the loss of weight followed the corresponding course. We thought that this indicated more than that the patient said he had tension and began to gain weight.

Delayed Favorable Effects in Psychotherapy.
DR. JOSEPH C. YASKIN.

Delayed beneficial effects in psychotherapy are observed in five categories of patients: (1) psychoneurotic persons who at the time of treatment reject psychic factors as causes of their symptoms; (2) psychoneurotic persons who accept emotional factors as causes of their difficulties but whose progress in treatment is unsatisfactory; (3) patients under considerable external stress and strain; (4) patients with psychoneurotic conditions complicated by organic disease, and (5) patients with certain constitutional psychopathic states.

The causes of delay in improvement or recovery in these patients are related to the several mechanisms in psychotherapy. The fundamental process in psychotherapy is one of emotional equilibrium, whereas the intellectual component is usually of secondary importance. Even in the case of patients treated by the prolonged free association method the final insight is largely emotional. Successful psychotherapy begins with the acceptance on the part of the patient of the concept that emotional factors can produce physiologic disturbances and difficulties in adjustment. The technic of psychotherapy depends to a large extent on transference, which is an emotional relationship.

The patients who at the beginning reject psychic factors as causes of their disability, patients under considerable external stress and strain and patients with conplicating organic disease may terminate the initial psychotherapy with dissatisfaction, and even resentment, but later may have a change of attitude conducive to more satisfactory rapport, perhaps in the hands of another psychotherapeutist. The initial therapy, though rejected, often leaves a definite impression and acts as an "inoculation."

The patient who willingly accepts psychic causes but fails to make satisfactory progress by reason of the inherent difficulties of emotional exploration and equilibration often discontinues the treatment but nonetheless already has procured some vague feelings and formulations regarding psychologic mechanisms and often unwittingly continues a self analysis leading to a more satisfactory evaluation and a better adjustment.

DISCUSSION

DR. K. E. APPEL: Dr. Yaskin has pointed out some interesting types of cases in which delayed favorable results of psychotherapy certainly appear. Many times we psychiatrists set the ball rolling and our patients go on to work out their problems themselves. We help them over acute stresses; and if they cannot continue therapy, they have to carry on their own treatment. A great many patients do so with reasonable effectiveness. I have even seen patients with psychoses who have been making pretty poor adjustments but who, when they break off therapy for some reason, have been able to carry on when they were thrown on their own and have got something out of their relationship with their physician. I should extend the group of patients which Dr. Yaskin mentions to include these.

I differ with Dr. Yaskin's statement as to the ineffectiveness of psychotherapy of the paranoid, manic-depressive and schizophrenic psychoses. There are certainly some patients who do not seem to be able to be touched by psychotherapy, but there are others, patients with paranoid conditions, schizophrenia and manic-depressive psychoses, whom I believe can be influenced by psychotherapy and can be helped, even independently of the drastic therapies.

I heartily agree with Dr. Yaskin in his emphasis on the emotional factors in psychotherapy. I believe that the processes of abreaction and of release are the most important tools in successful psychotherapy. I think that they are more important than intellectual understanding, intellectual formulations or the development of insight. It seems to me that many people live effectively and reasonably satisfactorily without the insight of normal people. If they are asked how they are living, or what they are living for, they cannot give a good account. The same is true of patients who recover from psychiatric disorders. Many recover without the development of insight; so it seems to me that insight is a condition which many normal people possess but which many normal people do not possess. It is also a condition which many patients acquire and many do not acquire, and I think that the striving for intellectual insight is a hindrance to effective psychotherapy.

DR. ROBERT A. MATTHEWS: Dr. Yaskin's paper should be reassuring, particularly to the young man who is starting out as a psychotherapeutist. He may feel frustrated when patients leave him and think that he accomplished nothing with therapy, but he may get delayed results.

DR. JOSEPH C. YASKIN: I want to call Dr. Appel's attention to the fact that psychotherapy was not useless in treatment of psychoses but was of limited value. We psychotherapeutists are helpful to our depressed patients. We encourage them and keep them as much as possible from attempting suicide. In a survey I made among my colleagues ten years ago concerning the prevention of recurrences of the manic-depressive psychosis, I did not get a satisfactory answer. We benefit people here and there, but a great deal more is to be accomplished. Six electric shock treatments do more for a patient with involutional melancholia than four years of psychotherapy. In my paper I have stressed the fact which Dr. Matthews has brought out, namely, that it is good not only for the younger men but for the men who are really doing the work, to be reassured.

"Acting Out" as a Defense Mechanism: Report of a Case. Dr. Gerald H. J. Pearson.

The analysis of an episode illustrating the mechanism of "acting out" was presented from the case history of a woman aged 28 who was suffering from major hysteria. While in the state hospital, she had barricaded herself in her room and then, with great effort, had secured three electric bulbs from the ceiling. She sat behind her bed with the three bulbs beside her. When the nurses broke into the room, she attacked them. At times during her analysis she imitated a dog and for long periods refused to stay on the couch, insisting on sitting on the floor close to the analyst.

These three forms of behavior were dramatic representations of the memories of her actions and feelings during her brother's birth, when she was 5 years old. When she first came for analysis, she had no conscious recollection of her mother's pregnancy, of her brother's birth, although she was in the house when it occurred, or of her brother as a baby. All of these memories were recovered during the analyses of the three forms of behavior just mentioned.

The case material illustrates that acting out is a frequently used mechanism whereby the recollection of memories of important childhood experiences is avoided.

DISCUSSION

Dr. J. C. Yaskin: What was the final result in this case?

Dr. Gerald H. J. Pearson: The condition improved, but the patient is not completely well.

Psychotherapy and Public Education. Dr. O. Spurgeon English.

Psychiatry has been receiving increasing publicity in the past few years, with good results. But it is felt that even more enlightenment of the public would be beneficial. Some of the ways in which such enlightenment has already been brought about are the public knowledge of selective service screening processes, the high rate of emotional casualties resulting from the war, books and articles dealing with psychiatry and more frequent allusions to the psychiatrist on the screen and on the stage, notably in the play and moving picture "Lady in the Dark." Inasmuch as the patient goes to the psychiatrist rather uninformed as to how the psychiatrist proceeds and uninformed about human personality in general, it seems important to utilize the various means of public enlightenment, such as newspapers, books, the radio, the stage and the screen, to make clear to the layman something of the nature of personality makeup. Why can it not become common knowledge that human beings are universally to some degree selfish, envious, sensitive, fearful, thoughtless and stubborn? Why not give more widespread exposition to the emotions of love and hate and how they occur, not to mention the frequency with which they occur? If the origin and existence of emotions such as these became more common knowledge, the patient going to a psychiatrist for help would not have to spend so much time in defending himself and protecting his self esteem. He and the psychiatrist would have a more common working knowledge of what produces emotional difficulties. Time would be saved in psychotherapy, not to mention the advantage of more effective and lasting results.

DISCUSSION

Dr. A. H. Pierce: All can agree with the theme of Dr. English's paper. In the past the interest of the public has been stimulated in regard to physical illness, and a great deal has been accomplished in educating it as to the character of this form of illness and the needs for preventing or escaping its ravages. Unfortunately, the public, perhaps like many psychiatrists, puts mental illness in an entirely separate category, although no one can deny that the human being is body and mind combined and inseparable.

Wars, deplorable as they are, seem always to be accompanied with tremendous advances. I do not hold that these advances counterbalance the ravages of war, but it is fortunate that out of the wreckage some good may come. After World War I great advances were achieved in the psychiatric field. The whole of psychiatry became revivified and was placed on something at least approaching a scientific basis. With this war there will undoubtedly come far greater advances.

Now and the postwar period is the appointed time for psychiatry to make itself heard and understood. I think that all psychiatrists are in agreement about this; the question is what means can be utilized in educating the public. As I see it, psychotherapy and mental hygiene are really parts of the same problem, although the former might be considered more prophylactic and the latter more exclusively therapeutic in character.

It is almost an axiom that before the public can be educated, it must first become interested. Today there can be no question of a very considerable interest, partly stimulated by selective service and Army discharges. If one wants proof of this it is furnished by the many articles in the lay press and the attendance at meetings dealing with problems of mental health to which the public are admitted. The lay attendance at the mental hygiene lectures now being given by the Philadelphia County Medical Society may be cited.

The public has today become aware of the existence of psychiatric problems and, to a lesser degree, of the means by which they can best be met. It is beginning to understand the "why" of emotional and mental disturbances. It is largely up to psychiatrists to show how these disturbances can still further be prevented or overcome.

Dr. Thomas Wright: The Navy has made some good psychiatric moving pictures. Films such as these, if made available to the public, would do a great service to the cause of mental hygiene.

Dr. S. B. Hadden: It is my opinion that psychiatry is more than a therapeutic system. It is an educational discipline, and if we as psychiatrists accept the obligation to educate the public, a great deal can be accomplished. After all, psychiatry deals primarily with man's highest adjustment—his adjustment in the community. We can certainly indicate to the public that psychiatry has a contribution to make to humanity by teaching man how to live a fuller, more emotionally mature, existence.

Dr. O. Spurgeon English: I am delighted at the enthusiasm with which you have received these ideas. I trust that when the Chinese said, "One picture is worth a thousand words," their statement was meant to include a moving picture. The moving picture is a wonderful means of reaching a large group of people in a way that affects their emotions. The moving picture, the radio and the stage are probably the most vital means of informing the public of the therapeutic values inherent in psychiatric interviews. In

group psychotherapy, for instance, one of the factors that is known to be valuable is the patient's realization that he is not the only one who is having trouble with his feelings and his ideas. The office psychotherapeutic situation runs into the danger of becoming an isolated one, with the patient too likely to feel that he is the only one who suffers from his particular dilemma. If, through more public enlightenment, both patient and psychiatrist could allude to the current treatment of a human problem by the moving picture, the radio or the stage, their mutual task would be considerably easier.

CHICAGO NEUROLOGICAL SOCIETY

ROBERT C. HAMILL, M.D., *President, in the Chair*

Regular Meeting, Nov. 14, 1944

Traumatic Glossopharyngeal Neuralgia. DR. HAROLD C. VORIS, Chicago, and (by invitation) LIEUTENANT J. T. BAKODY, MC (V), U.S.N.R.

In June 1944 a Marine sergeant aged 23 was injured in combat by mortar shell fragments. One fragment entered below the left external ear, just anterior to the mastoid process, traversed the structures of the neck in the lateropharyngeal space and entered the pharynx through the tonsil. The patient actually spit out the shell fragment from his mouth. There was considerable bleeding but no loss of consciousness. He stated that there was immediate paralysis of the left side of the face and that after the injury intermittent pain developed on that side of the face, which has persisted up to the present time. Swallowing, chewing, coughing and sneezing precipitate the attacks of paroxysmal pain. The pain seems to begin at the left malar eminence and radiates into the left eye and left ear; it is severe and lancinating and lasts twenty to thirty seconds. An apparent autonomic concomitant, with unilateral flushing of the lower part of the face, has been observed. More recently the pain in the ear has become more prominent, with prickling sensations deep within the ear.

The physical findings are essentially normal except for those referable to the left side of the head. There is a healed shrapnel wound of entrance just below the lobule of the left ear, while the wound of exit is a small opening, about 1 cm. in diameter, at the anterosuperior pole of the left tonsillar fossa. Partial tonsillectomy has been accomplished by the shrapnel in this area. Stimulation of the left tonsillar region with an applicator reproduces the characteristic pain. On the other hand, cocainization of the left tonsillar area abolishes the trigger zone, and the pain cannot be reproduced while the cocaine is effective. The tenth, eleventh and twelfth cranial nerves are apparently normal. There is slight residual paresis of the lower left side of the face of peripheral type. Roentgenographic studies are normal for the skull, the mastoid region and the left styloid process.

DISCUSSION

DR. HAROLD C. VORIS: The radiation of this patient's pain, as described, is not exactly typical of that described as glossopharyngeal neuralgia. However, the abolition of the trigger area is quite characteristic. Neuralgia of the fifth cranial nerve is much more common than glossopharyngeal neuralgia. Traumatic injury of the fifth nerve is also relatively common. As a matter of fact, the supraorbital branch of the fifth nerve is the most frequently injured cranial nerve because of the frequency of supraorbital laceration. Injury of the maxillary nerve is usually the result of injury to the facial bones. The maxillary nerve may be injured in cases of fracture of the maxilla. Likewise, injury of the mandibular nerve is more frequent with fractures of the mandible than with injuries to the base of the skull. However, both these nerves may be injured in connection with basal skull fracture.

I had a patient with a basal skull fracture who was operated on for a hemorrhage of the middle meningeal artery. When he regained consciousness, he had anesthesia of the mandibular nerve, which was persistent. I have seen only 2 cases of paroxysmal facial pain (both in the maxillary distribution) in which the picture conformed to the classic syndrome of trigeminal neuralgia and seemed to bear a definite relationship to a previous basal skull fracture. Both patients had onset of pain within six to twelve weeks after injury, and both were relieved, temporarily, by injection of alcohol into the maxillary nerve. I did not see them again and do not know whether the pain recurred, as is always the case with true trigeminal neuralgia. Certainly, there is an unusual combination of circumstances in this case—first, the isolated injury to the glossopharyngeal nerve and, second, the prompt appearance after the injury of neuralgia, which I believe is true glossopharyngeal neuralgia.

DR. PETER BASSOE: I understand this patient had some redness of the face, and I should like to ask whether he noticed that his face perspired and became red after eating. If so, one might think that the auriculotemporal nerve was involved. This injury is often associated with facial palsy and involvement of other nerves to the face. The patient says he did not; so that settles it.

DR. R. P. MACKAY: I should like to ask whether the trigger zone was definitely located. It is insufficient to say that coughing, sneezing or swallowing produced the pain, for these activities stimulate wide areas in the mouth, extending far beyond the area innervated by the glossopharyngeal nerve.

DR. HAROLD C. VORIS: When I saw this patient, he had had the tonsillar fossa cocainized that morning and had been able to eat lunch comfortably. During the period of anesthesia of the trigger area it had been demonstrated that stimulation of that area did not produce pain. At the time of my examination the effects of the cocaine had worn off, and stimulation of the tonsillar fossa produced the usual paroxysm of pain.

I presume the nerve injury is in the retropharyngeal space. I was asked whether section of the glossopharyngeal nerve in the neck was advisable. I stated that an attempt at exploration in the neck, because of the possibility that the injury and resultant scar involved the great vessels, might be more dangerous than cranial section of the nerve. Moreover, peripheral section of the nerve cannot be expected to give permanent relief, while cranial section will do so.

Effects of Penicillin on the Central Nervous System. DR. HERBERT C. JOHNSON, DR. A. EARL WALKER and DR. THEODORE J. CASE.

DISCUSSION

DR. CLARENCE NEYMANN: Through the Commercial Solvents Corporation, Dr. Heilbrunn and I were presented with a large amount of penicillin for experi-

mental purposes. We have used this drug in treatment of patients with far advanced dementia paralytica at the Chicago State Hospital. At first the drug was administered intravenously and intramuscularly. Later it was injected intracisternally. Five patients were treated with approximately ten daily intrathecal injections of penicillin. The first patient, who was given too great a dose (100,000 units) exhibited a state similar to that shown in the moving picture of the cat. After an initial period of severe headaches and restlessness, there developed tenseness and muscular twitching, ending in generalized convulsions. His life was saved with some difficulty by placing him in an oxygen tent and quieting him with sodium amytal and morphine. After twenty-four hours he recovered.

The purity of the drug seems to influence the reaction. In the beginning any dose above 30,000 Oxford units of penicillin of 25 per cent purity given daily produced tenseness, twitchings and, finally, convulsions. At present we are giving up to 40,000 units of penicillin of 40 per cent purity without serious complications. We have been promised crystalline penicillin; this may solve the problem. It seems that there is some relation between the amount of the impurities and the severity of the reaction.

As in the animal experiments, the cell count of the spinal fluid in man rises abruptly; red blood cells appear in the spinal fluid, together with polymorphonuclear cells and lymphocytes. We are not prepared to say whether the patients will benefit from this therapy. However, the colloidal gold curve has shown a tendency to flatten out to normal. The penicillin disappears from the spinal fluid in twenty-four hours. No penicillin enters the spinal fluid if the drug is injected intravenously or intramuscularly, even in huge quantities. With the intrathecal method of administration we have noted no convulsions or other serious complications. Therefore the purity of the product used experimentally by the authors is of great interest.

Extradural Hemorrhage: Report of a Case. DR. A. VERBRUGGHEN.

A man aged 75 was admitted to the hospital six hours after falling 4 or 5 feet (1.2 or 1.5 meters) onto his buttocks. He rose, walked to the house, climbed fourteen steps, sat down on a chair and during the course of the next half-hour lost complete control of his legs. This paralysis was associated with excruciating pain in the arms and back and with numbness from the nipple line downward. He was examined six hours later, when he showed complete paraplegia with loss of sensation below the nipple lines, absence of reflexes, a bilateral Babinski sign and urinary retention. There was an uncertain sensory level at the seventh or eighth cervical segment on the hand. There were movement in the upper extremities, weak extension and fairly strong flexion. The biceps reflexes were present bilaterally, but the triceps reflexes were not obtained. Spinal puncture could not be carried out because of long-standing arthritis of the spine of Marie-Strümpell type. Roentgenograms of the cervical portion of the spine did not reveal any fracture dislocation.

Because of the history of progressive symptoms, operation was immediately undertaken; beneath the fifth and the sixth and part of the seventh cervical lamina was found an extradural clot, measuring 5 by 2 by 1 cm. When this was removed, the dura pulsated freely. The wound was closed rapidly, and the patient was sent back to bed. The following day the level had descended to the tenth thoracic segment, and there were very faint movements in the legs. By the third postoperative day the sensory level had descended to the knees, and there were more powerful movements in the legs. By the fourth postoperative day sensation to pinprick was restored over the entire body, and all muscular movements could be performed in the legs, although they were weak. During the course of the next ten days the patient regained ability to void and the catheter was removed; he was sent home, where he made an uninterrupted recovery. The case is reported because of its rarity. A review of the literature reveals little convincing evidence of similar cases. In the cases reported the hemorrhages were either traumatic or spontaneous.

DISCUSSION

DR. VICTOR E. GONDA: An extradural hemorrhage would have to be fairly large and hard to press on the dense dura mater and compress the spinal cord completely. The question arises whether early evacuation of the blood in a case of suspected extradural hemorrhage would not prevent serious and irreparable damage.

DR. J. P. REICH: I remember a case in Breslau, Germany, many years ago. A young boy, while playing the piano, suddenly had a terrific pain in the back. A physician, who was immediately called, found flaccid paralysis of both legs. When a neurologist arrived, after a short time, the paraplegia had disappeared completely. The diagnosis of epidural hemorrhage was made, and the rapid disappearance of the motor disturbance was explained by the flowing of the blood down into the lowest part of the dural sac. According to a personal communication which I received from a co-worker of Prof. Otfried Foerster, it is possible in such cases to remove the blood by a needle introduced into the sacral portion of the canal.

DR. A. VERBRUGGHEN: With regard to Dr. Reich's comment, I do not understand how hemorrhage could occur in the cervical region and the blood be removed by inserting a needle into the sacral hiatus. It is difficult to understand how one could be sure that there was blood to be found or why it would track down from the cervical to the sacral region or why, if it did, it should be removed.

I do not believe that Dr. Gonda is suggesting that all patients with injuries to the spinal cord should be operated on at once for fear there might be an extradural hemorrhage; extradural hemorrhage is an extremely rare condition, and this is the first case I have seen in fifteen years of neurosurgical practice. The mechanism is probably that of pressure on the spinal cord produced in much the same way as pressure from extradural hemorrhage is exerted on the brain. The coagulation of the blood probably causes some reaction in the spinal cord. In this case spinal shock was present, though the paralysis came on slowly. There is no remedy for this mechanical compression of the spinal cord except mechanical removal. The picture would be further complicated if, in addition to a fracture dislocation which was not causing compression of the cord, an extradural hemorrhage occurred which did cause compression of the cord; in such a case, however, the progressiveness of the symptoms would be of the utmost importance.

In the case of traumatic hemorrhage described by Jonas there was no fracture dislocation, but the surgeon

merely operated at the level indicated by the sensory level. However, in 2 other cases described in the literature it was apparent that the hemorrhage was spontaneous. One cannot be sure from perusal of the history, of course, whether a careful postmortem examination was made or not. In 1 instance, however, an 18 year old housemaid had had difficulty at stool in the morning. Half an hour later she experienced great pain in her arms. In two hours she had complete paralysis of the upper and lower extremities, and in two hours and a half she died of respiratory failure, with an extradural hemorrhage beneath the second and third cervical vertebrae. In another case a man, while shoveling snow, experienced a wrenching of his back and over the period of the next twenty minutes felt weakness in the legs. During the course of the next twenty-four hours one leg recovered, but the other was still paralyzed; in the meantime he had urinary retention, and he finally died on the fourth day after this spontaneous injury. In this case an extradural hemorrhage was found in the lumbar region of the spinal cord. In the case of the young woman the pathologist stated that he had rarely examined more healthy organs. The question whether any of these patients may have had hemophilia was not entered into.